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THE UNITED STATES ARMY'S WAR IN THE AIR AGAINST THE MOSQUITO-BORNE DISEASES.*

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Our war in the air rarely makes the front page of the newspaper; nevertheless it is a major conflict, which began half a century ago and is still being waged on many fronts at home and abroad. For the benefit of any pacifistic friends who may be present I hasten to add that this is a war of defense. It has been fought, not with airplanes and high explosives, but with test-tubes and steam shovels, microscopes and Paris green, quinine cocktails, and native battalions, clearing the muck from jungle swamps. In other words, my title refers to the fight of the Medical Corps against the mosquito-borne diseases.

As this fight is a part of the campaign waged against all infectious diseases, I will digress a moment to indicate some of the purposes of this broader campaign. The primary objective of the Medical Corps is to safeguard the health of the soldier and keep him physically fit, especially during periods of national emergency. In the attempt to accomplish this, the civil profession has always been called on for help. The best available medical and surgical care has been given the sick and wounded, and every effort has been made to prevent infectious diseases. Both of these activities are essential, but the latter is more important to the conservation of man power.

Throughout history, epidemics have been the scourge of armies operating in the field, and prior to the development of modern pre-

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ventive medicine, the infectious diseases consistently caused more disability and death than did battle injuries. In fact, they frequently decided the outcome of important wars.

Considerable progress has been made in the attempt to protect the soldier, but much remains to be done. During our various wars of the past the following proportions of the total deaths were caused by disease:[1,43] Revolutionary War, 90%; Mexican War, 84%; Civil War, 62%; Spanish American War, 87%; and World War, 50%. In the Civil War, disease was responsible for more than 224,000 deaths in the Union force of 2 million men; on the other hand, during the World War there were only 50,000 disease deaths in our army of 4 million men. In the latter conflict, the respiratory infections predominated, and for these we still have no satisfactory methods of control. The prevalence of the intestinal group of diseases was relatively low, and typhoid was unimportant due to improvements in field sanitation and the use of "triple-typhoid" vaccine. Smallpox was eliminated by vaccination. Certain other important infections caused little or no trouble, but only because they were not endemic in the regions occupied by our troops. The latter group included some of the diseases transmitted by mosquitoes.[22]

The army's struggle against mosquito-borne diseases began under the leadership of G. M. Sternberg, a pioneer scientist, who was referred to by Robert Koch as the "Father of American Bacteriology."[25,41] In 1916, your A. C. Abbott paid tribute to Sternberg's influence on the development of preventive medicine in this country and expressed appreciation of his good fortune at having served as assistant to this able man.

Sternberg entered the army during the Civil War, and served with distinction on many battlefields. Early experiences with epidemics of typhoid, cholera, yellow fever and malaria created in him an intense interest in the then young science of bacteriology, and a lifelong desire to prevent the military plagues. In 1880, his translation of Magnin's book on bacteriology constituted the first American text on this subject, followed in 1892 by his own more extensive "Manual of Bacteriology." During his long service he had several opportunities to investigate yellow fever, and by careful bacteriologic studies he disproved the claims of various workers who believed they had discovered the causative agent. In 1881, he refuted the claims made for the "Klebs-Tommasi-Crudilli" bacillus as the cause of malaria; and 4 years later, at Johns Hopkins University, he demonstrated for the first time in America, the living plasmodium of malaria. During the period from 1893 to 1902 Sternberg's duties as Surgeon General of the United States Army, interfered with his personal laboratory investigations, but afforded opportunity to develop in the Army his ideas concerning the importance of experimental studies in dealing with military diseases. At an early period he established the Army Medical School, organized laboratories in

army hospitals, and in every way possible stressed the importance of medical research.

After the Spanish American War, General Sternberg ordered the formation of special boards of officers for the investigation of the important diseases in our newly acquired tropical possessions. Major Walter Reed and his associates were sent to Cuba, where they discovered the mosquito transmission of yellow fever. Lieut. B. K. Ashford proved that the malignant disease, "Puerto-Rican" anemia, was due to massive hookworm infection, and began a campaign of control, which was the forerunner of the world-wide eradication program of the Rockefeller Foundation. The third board was established in the Philippine Islands under Lieut. R. P. Strong, now of the Harvard Medical School, and he, and those who succeeded him, contributed to our knowledge of various diseases, including dysentery, plague, beri-beri, filariasis, surra, malaria, and dengue fever.[47] This latter board existed in Manila until 1934, when it was transferred to Ancon, Panama Canal Zone, where its members are now engaged in the study of malaria and other important diseases. Many of these tropical infections are of relatively slight importance to the army under present conditions, but some are potentially dangerous, and might seriously cripple a military force required to operate in regions where they are prevalent. This applies particularly to yellow fever, dengue fever and malaria.

Yellow Fever. Yellow fever has existed in the American tropics for at least 4 centuries, and during the past it has frequently invaded the temperate regions in the summer months. It is rarely severe among the adult natives of endemic areas apparently because a large proportion of such individuals become immunized through mild, childhood infection. However, among non-immune adults, either visitors from abroad or the inhabitants of newly invaded regions, it may cause explosive epidemics with high morbidity and mortality.

Before the present century, destructive outbreaks of yellow fever were frequent among European troops operating in the West Indies and in South and Central America. A spectacular example occurred during the revolt of the blacks in Haiti, when a veteran French Army was practically annihilated:[1] In 1802, a force of 58,545 troops embarked at Brest for Santo-Domingo, and within 4 months 50,270 were dead, chiefly of yellow fever. Of the 8000 remaining 3000 were sick or wounded. In 1809, this army was reduced to 300 men, who returned to France. In the United States alone there have been more than 100 epidemics. Most of these occurred in the South; but on many occasions yellow fever appeared in our northern cities, including Philadelphia, New York, and Boston; and even invaded Canada. It is estimated that the disease caused at least 100,000 deaths in this country. During the brief war with Spain, 1300 cases of yellow fever occurred in our troops, and caused 200 deaths.

In 1900, Walter Reed went to Cuba with instructions to investigate yellow fever and to determine the etiologic significance of Sanarelli's *Bacillus icteroides*. The bacillus was soon ruled out, and Reed's well known human experiments were begun, to test Dr. Carlos Finlay's[14] belief in the mosquito transmission of yellow fever. After 12 months of heroic work it was proved that the disease is transmissible by *Aëdes ægypti* and the mechanism of its transmission was determined.[26] This information was immediately applied by the Governor of Cuba, General Leonard Wood, who ordered an intensive campaign against mosquitoes, which was effectively carried out by Colonel William Gorgas. By 1902, the city of Havana which had been cursed with yellow fever for more than 150 years, was for the first time free of this disease. Similar control work was soon done elsewhere, and within a few years the United States, the Panama Canal Zone, and many tropical regions were likewise released from the yoke of yellow fever.

By 1914, it appeared that the disease had been eliminated in all but a few endemic foci, including one in Ecuador and possibly others in Mexico and West Africa. Acting on the advice of General Gorgas, the Rockefeller International Health Board therefore undertook a campaign which had as its purpose the eradication of yellow fever from the face of the earth. In 1918, a commission was sent to Guayaquil, and after 6 months of Aëdes control work, the disease disappeared from that region. Incidentally, it was here that Noguchi,[24] questioned Reed's discovery that yellow fever is due to a filtrable virus and reported *Leptospira icteroides* as the cause. This mistake was rectified 10 years later by the work of Sellards[33] and others. Subsequently, outbreaks of yellow fever appeared elsewhere in America, but as they were controlled within a short time, it was still thought possible to stamp out the disease.

In 1920, the Rockefeller Foundation sent to West Africa an expedition headed by General Gorgas. He died in London, but his assistants carried on, and finding evidence of the existence of yellow fever, they recommended further studies. In 1925, General F. F. Russell, who was recently retired as Director of the International Health Board, sent out a second expedition, under Major Henry Beeukes, to work in Nigeria and on the Gold Coast. After 2 years of intensive search for an experimental animal, Stokes, Bauer, and Hudson[42] (1927) found that monkeys (*Macacus sinicus* and *M. rhesus*) from non-endemic countries were susceptible to infection. This fundamental discovery has made possible many advances in our knowledge of the disease.

Since that time, 32 mosquito species of the genera: *Aëdes*, *Culex*, *Mansonia* and *Anopheles*, have been incriminated as yellow fever vectors, and certain flies, bedbugs and ticks have been shown to be mechanical carriers of the virus.[11] In 1929, Sawyer, Lloyd, and Kitchen[30] developed a method for the preservation of yellow fever

virus, by drying it in a vacuum while frozen, thus making it possible to transport the virus to research laboratories in America. In 1930, Theiler[44] showed that white mice are susceptible to intracerebral injections of virus, and this afforded a more convenient experimental animal. The following year, Sawyer and Lloyd[29] (1931) developed the so-called mouse "protection test" which is now being used in a world-wide immunity survey. Recovery from an attack of yellow fever is followed by the appearance of virus-neutralizing antibodies, which remain in the serum throughout life. Therefore the "protection test" can be used to determine the periods during which the disease has existed in any community.

The use of this test supplemented by pathologic methods, has recently led to the discovery that in certain countries, where yellow fever has been eliminated from the towns and cities by mosquito control, the disease still exists in sparsely settled jungle regions, in spite of their freedom from *Aëdes ægypti*. Soper,[40] who has studied this jungle type of yellow fever since 1932, reports that although urban outbreaks may decline or cease for a time there is a vast, previously unknown, reservoir of infection in the interior of South America. The endemicity of the disease, instead of being limited to a few scattered areas, as was once thought, extends over large parts of Brazil, Bolivia, Paraguay, Peru, Ecuador, Venezuela and Columbia. Last year, during a survey made of Indians in the San Blas Islands about 50 miles from Colon, members of the Army Medical Research Board, Ancon, C.Z., found an individual less than 10 years old who gave a positive protection test.

Recognition of the existence of jungle yellow fever naturally has caused the Rockefeller Foundation to abandon its original program of world eradication, based on the destruction of Aëdes in key centers,[28] and has introduced many new problems such as: 1, a search for the still unknown vectors and hosts of the jungle infections; 2, methods to protect individuals exposed in endemic regions; and 3, precautions against the spread of the disease from the jungle areas to "Aëdes-infested" urban centers. Such spread has been traced in a few outbreaks in Brazil and Bolivia. The increasing facilities for rapid transit make it important to guard against more serious accidents.

With this in view the countries concerned have adopted mutually protective agreements and the Pan-American Airways system is taking special precautions to avoid accidental transportation of infected mosquitoes or passengers. These precautions will include: 1, the vaccination of all flying personnel as soon as practicable; 2, careful inspection of passengers to eliminate those infected and, 3, systematic destruction of mosquitoes on all airplanes.

Recent experimental work on yellow fever vaccination indicates that eventually a prophylactic suitable for military use may become available. The vaccine of Theiler and Smith[46] (1936) which is

prepared with an attentuated strain of tissue-culture virus, protects lower animals and is now being used in man.

For over 30 years the United States Army has enjoyed an armistice with its ancient foe, the Yellow Jack, but we must be prepared for a renewal of hostilities at any time. Yellow fever could easily cause serious damage, should it be introduced into the United States during the summer, or should it become epidemic among troops operating in an endemic region. If we are to protect our forces under field conditions, some effective method of immunization must be made available. It is hoped that this may be accomplished by the "Theiler-Smith" vaccine.

Dengue Fever. Dengue, or break-bone fever, is a non-fatal disease of some military importance. It is endemic in warm climates throughout the world, and often occurs in extensive epidemics. One of the earliest clinical descriptions of the disease was contributed by the distinguished Benjamin Rush, of this university, who was responsible for the medical organization of the Army in 1777. His studies on dengue were made during a severe outbreak which occurred in Philadelphia in the summer of 1780.

The transmission of dengue is, in many ways, similar to that of yellow fever. The work of Graham[16] (1903) in Syria indicated its mosquito transmission, and later studies of Bancroft[3] (1906) and of Cleland, Bradley, and McDonald[9] (1917–1919) incriminated *A. ægypti*. Various members of the Army Board in Manila have added to our knowledge of dengue. In 1907, Colonels Ashburn and Craig[2] proved that it is caused by a filtrable virus in the blood; and they transmitted it mechanically through *Culex fatigans*.

Colonel J. F. Siler and his associates[35] (1925–1928) carried out extensive studies of dengue transmission by *A. ægypti*. Their conclusions have been summarized as follows:

"*a*. Previous reports of the transmission of dengue fever by *Aëdes ægypti* were amply confirmed (47 instances).

"*b*. *Culex quinquefasciatus* was eliminated as a possible transmitting agent (7 attempts to transmit all of which were negative).

"*c*. The patient with dengue fever can infect the mosquito in the late incubationary stage of the disease (6 to 18 hours prior to the onset of symptoms, as manifested by elevation of body temperature above normal) and ordinarily continues to be infective to Aëdes mosquitoes during the first 3 days of illness.

"*d*. When the mosquito draws blood from an individual during the first 3 days of his illness, under conditions ordinarily encountered in nature, the virus must remain in the mosquito for a somewhat definite period of time before the mosquito is capable of infecting a human being through its bites. Under the conditions existing when the Board carried out its experiments (cool, dry season in the tropics), this time interval was found to be from 11 to 14 days.

"*e.* After the infected mosquito has become capable of transmitting the virus to human beings it retains that capacity throughout the remainder of its life (experimental dengue in humans was produced with mosquitoes infected 62, 66 and 75 days previously).

"*f.* The virus causing dengue fever is not carried from the infected mosquito through its eggs to the next succeeding generation.

"*g.* For all practical purposes the incubation period of dengue fever in human beings may be considered as being from 4 to 6 days, inclusive.

"*h.* An attack of dengue is followed by a period of increased resistance to the infection (at least for several weeks or months), but the duration of the immunity was found to be exceedingly variable. There was no evidence of racial immunity. The permanent population living in areas of endemicity develops a high degree of immunity, the most logical explanation being that it results from somewhat frequent, repeated, mild attacks."

Schule[32] in 1928 observed that *A. ægypti* may become infective as early as the 8th day after ingesting dengue virus, when the atmospheric temperature and humidity are relatively high. Later Army workers (Simmons, St. John and Reynolds[38]) investigated the disease with the following results:

a. Aëdes albopictus, a common oriental mosquito, was shown to be an effective biologic vector, the mechanism of transmission being similar to that for *A. ægypti*.

b. Dengue was transmitted mechanically from individuals in the acute stage of the disease to susceptible persons, through interrupted feeding of either *Culex quinquefasciatus* or *A. ægypti* provided large numbers of mosquitoes were used.

c. The virus in the mosquito was shown to be filtrable.

d. Virus was transmitted from infected to normal mosquitoes without passage through a mammalian host.

e. Native Filipinos living in mountainous regions beyond the range of Aëdes were shown to be susceptible to dengue, while comparable groups of natives in endemic areas were highly immune.

f. It was shown for the first time that dengue could be transmitted through mosquitoes from man to certain species of monkeys caught in non-endemic regions and back to man. Adult monkeys of the same species from endemic areas were found to be immune. This suggested the possibility that a dengue "reservoir" might be maintained in uninhabited jungle areas by passage of the virus through the susceptible young of monkeys or other animals, as has since been shown to be the case in Jungle Yellow Fever.

g. Dengue virus failed to penetrate the excoriated skin of human beings.

h. Experimental observations indicated that dengue produces a somewhat high degree of immunity, certainly for a period of several months to more than a year.

i. A saline suspension of macerated infected *A. ægypti* used as a vaccine failed to confer demonstrable immunity.

In 1931, it was shown by Holt and Kintner[17] that in infected *A. ægypti* the virus is present in all parts of the body.

Much has been added to our knowledge of the virus of dengue and of the epidemiology and transmission of the disease by workers in various parts of the world, including: Cleland, Bradley and McDonald,[9] Koizumi, Yamaguchi and Tonomura,[19] Manoussakis,[21] Blanc and Caminopetros,[4] Blanc, Caminopetros and Manoussakis,[5] Blanc, Caminopetros, Dumas and Saenz,[6] Snijders, Dinger and Schüffner.[39]

The present importance of dengue to the army is due almost entirely to its high incidence among troops in the Philippines. For 37 years a large proportion of the soldiers, stationed in and around Manila, have contracted the disease at some period during their stay. The annual incidence curve has fluctuated at intervals which appear to be correlated with the importation of susceptible troops, and has shown no sustained improvement during this period. As most of the adult native residents of Manila are immune to dengue, and as yellow fever does not exist there, the civil authorities have not regarded complete Aëdes control as important enough to warrant its cost.

Dengue rarely kills, and is of relatively short duration, however it is a potential military hazard because of its widespread endemicity and its tendency to occur in epidemics which incapacitate large groups of persons within short periods of time. For example, in the summer of 1885, three-fourths of the inhabitants of Austin, Texas, were sick with dengue;[34] and in 1897, half the population of Galveston was infected. During the great epidemic of 1922 over a million people were attacked in our southern states; and during 1927–1928 about a million and a half cases occurred in Greece. We can all visualize conditions under which such an epidemic, striking during the critical period of a decisive campaign, might jeopardize the success of our armies. To avoid such an unfortunate occurrence an effective vaccine is needed for the protection of troops in the field.

Malaria. Among all the diseases of mankind, malaria deserves the unsavory title of "Public Enemy No. 1." We who enjoy the present, relative security of our northern cities, are apt to think vaguely of malaria as an interesting, but disagreeable, disease which is visited mainly on the lazy natives of southern climes. The fact of the matter is that these "shiftless natives" belong to a great tropical empire which stretches around the earth, and is peopled by millions who have been conquered and enslaved by malaria.

Sir Patrick Manson concluded that, "malaria causes more deaths, and predisposition to death, than all the parasites affecting mankind together;" and Osler designated malaria as the "greatest single destroyer of the human race." Today, in spite of our accumulated knowledge concerning its etiology, treatment and control, this dis-

ease exceeds all others in sapping the vitality, and impeding the social, industrial, and political progress of the inhabitants of many tropical countries.

The Army's experience with malaria has been largely satisfactory; and our relative success in its control has undoubtedly helped to develop a false sense of security. A century ago malaria caused more than 25% of the disease admissions to Army hospitals, while since the World War the proportion has been only 1%.

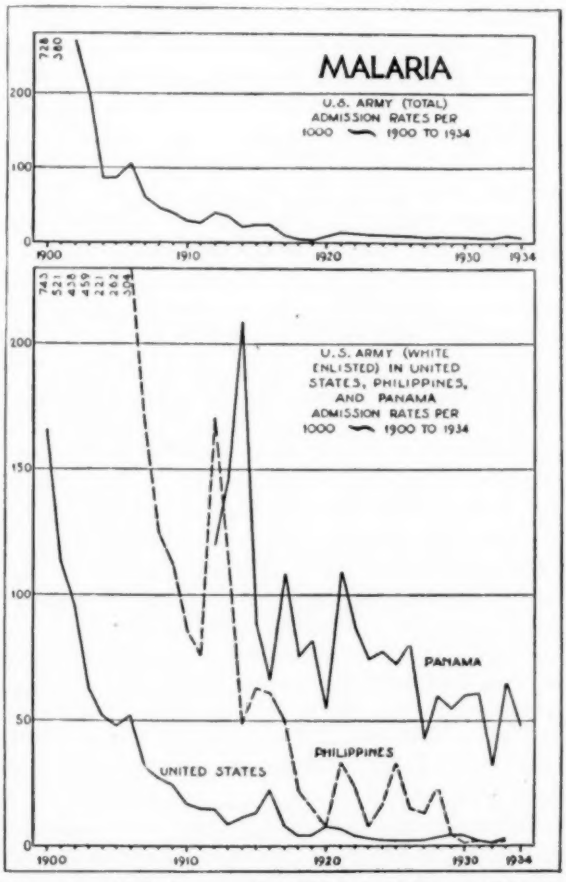

FIG. 1.—From unpublished manuscript, "Malaria in Panama," by Simmons, Callender, Curry, Schwartz and Randall, 1937.

The modern campaign against the disease began after 1898, when the studies of Manson, Ross, Grassi, and others had incriminated certain anopheles mosquitoes as vectors. The results are indicated by the annual admission rates per 1000 among white enlisted men, which are shown in Fig. 1.

As is indicated by the upper curve, the malaria admission rates for the total Army declined from 728 per 1000, in 1900, to 380 the next year; and since 1916 they have been almost negligible.[7] The incidence curve for troops in the Continental United States was the first to fall, the rates being about 165 per 1000 in 1900, 50 in 1907, and less than 10 since 1920.

Conditions were quite different in our Philippine stations, and during the early days a large proportion of our troops there contracted malaria. The rates decreased gradually from a high of 743 per 1000 in 1900, to less than 50 in 1918, and since 1930 they have been negligible. The present low incidence affords spectacular proof of the value of the experimental studies of Colonel C. F. Craig[10] and others, and to the effective field work of many Army sanitarians.

The experience of our troops in the Panama Canal Zone has been less satisfactory. The trend of the malaria incidence curve has been downward, but even as late as 1933 the rate was 65.9, which was 20 times the rate among troops in the United States, and 34 times the rate for our white soldiers in the Philippines.[43] This comparatively high incidence of malaria among the soldiers in Panama may be due in part to differences in the mosquito vectors of the regions concerned. In the Philippines, the important vector is *Anopheles minimus*, a mosquito which breeds in rapid, foot-hill streams, above sea level. In Panama, the chief carrier is *A. albimanus* and there are several other effective vectors, some of which prefer to breed in sunlit, still waters, others in well shaded jungle streams, and still others in tidal swamps, thus rendering their control more difficult and costly. Before 1934 only 4 of the 15 recognized anophelines of the Canal Zone were known to be malaria vectors, and since that time, Rozeboom[27] of the Gorgas Memorial laboratory has incriminated *A. bachmanni* and Simmons[36] of the Army Board has incriminated 4 additional species, including *A. punctimacula*.

Since the early days of the Spanish Conquistadores, the Isthmus of Panama has been notorious for its pestilential fevers, especially yellow fever and malaria. Both of these plagues, but mainly malaria, contributed to the failure of DeLesseps' attempt to build the French canal, during which at least 20,000 lives were lost and more than 260 million dollars were spent.

In 1904, when Gorgas began his well-known sanitary campaign[15] which made possible the construction of the present canal, he was armed with the knowledge that malaria is transmitted by anopheline mosquitoes. Also he had practically unlimited funds to use for mosquito control. As shown in Fig. 2, the malaria rates among canal employees decreased from a high of 821 per 1000 in 1906 to a low of 16 in 1916.[7] By continuing the anti-mosquito work at a present cost of about $130,000 annually, this decrease in malaria has been maintained, but there has been no progressive improve-

ment during the last 20 years. As shown in Fig. 2, the malaria rates among troops are much higher than those for canal employees.

The persistence of malaria in the Canal Zone, in spite of the vigorous measures taken to prevent it, indicates the difficulty of mosquito control in the American tropics. The relatively large annual appropriations have been sufficient only to eliminate the

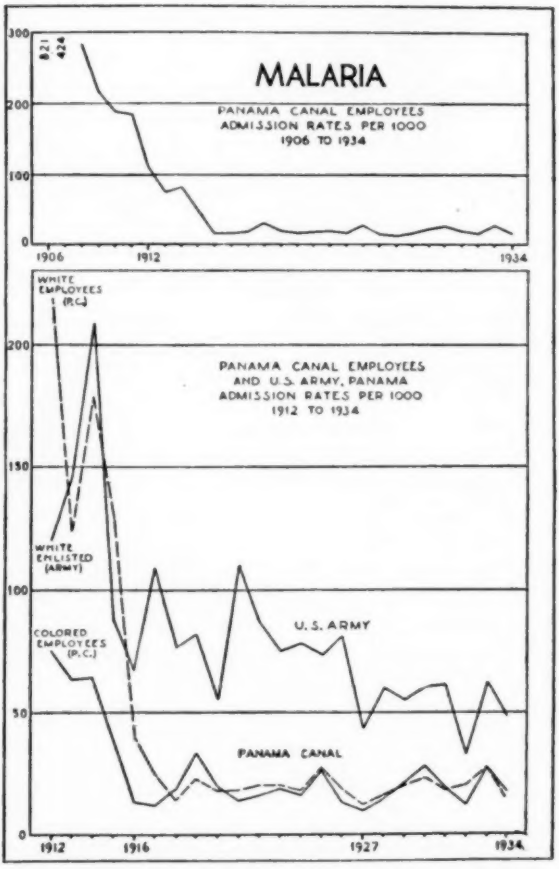

FIG. 2.—From unpublished manuscript, "Malaria in Panama," by Simmons, Callender, Curry, Schwartz and Randall, 1937.

mosquito breeding in small areas, which extend for 1 to 3 miles around the cities of Colon and Panama, the Canal Zone towns and the permanent military posts (Chamberlain)[7]. These areas are surrounded by a great unsanitated region including the rest of the Zone and the Republic of Panama, in which mosquitoes continue to breed unhindered. From these vast breeding places, many anophelines

invade the sanitated areas each year, coming either in nuptial flights or in search of blood (Curry[12]).

Malaria is highly endemic among the natives living in and around the Zone, and the incidence of human carriers is high (Clark and

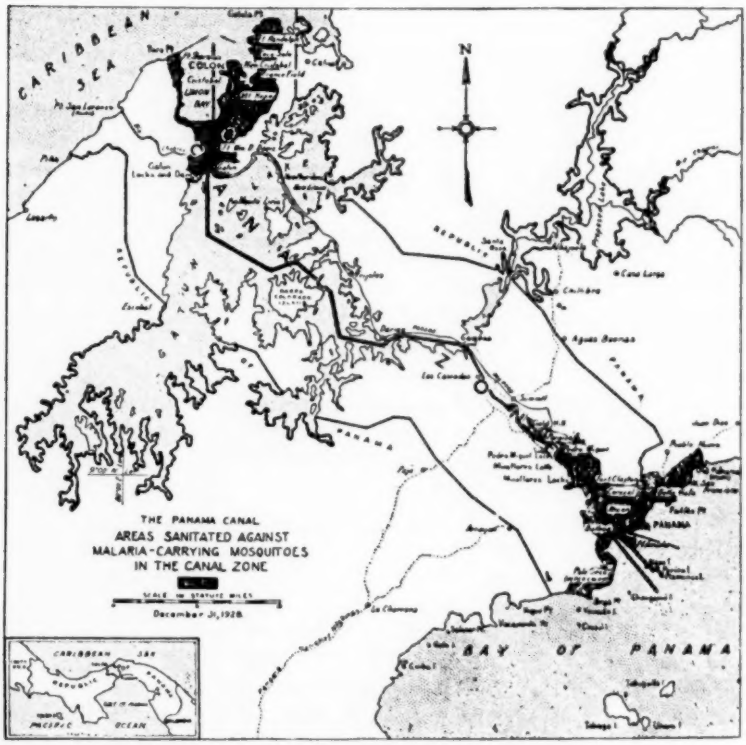

FIG. 3.—The channel of the Canal is represented by the heavy black line from Cristobal and Limon Bay on the Caribbean side to Balboa and Panama Bay on the Pacific side. The two lighter lines, at a distance of 5 miles on either side of the Canal, are the boundaries between the Canal Zone and the Republic of Panama. The Canal Zone also includes all of Gatun Lake, together with a narrow border of land around it, and the basin of the proposed lake in the upper Chagres River basin. The total area sanitated against malaria is shown in heavy shading about the two terminals of the Canal. Within these sanitated areas are concentrated the bulk of the Canal employees, as well as the military forces and their families. Elsewhere in the Canal Zone practically all employees and their families are furnished thoroughly screened quarters, but no antimosquito work is carried out. Farmers, known as "Zone settlers," live outside the sanitated areas and are unprotected against malaria. (From the official records of the Health Department of the Panama Canal.)

Komp[8]). Therefore the invading mosquitoes have many opportunities to become infected before their arrival. Surveys made by the Army Board during the past 2 years show that a significant proportion of the Anopheles caught in barracks are infected.

The greater prevalence of malarial fevers among the troops,

compared with Canal employees, is probably due to various factors, including the following: 1, the soldiers may be more susceptible as they are young, white adults who remain in Panama only 2 or 3 years, while over 50% of the employees have lived there for 10 or more years, and may have developed some resistance to the infection; 2, most of the Army posts are located nearer the unsanitated jungles than are the Canal Zone towns; and are nearer mosquito breeding areas; 3, the soldiers are exposed to mosquitoes, not only in the sanitated areas, but also while on reconnaissance trips and maneuvers in unsanitated regions.

During such periods of exposure, special precautions are taken to prevent malaria.[43] The men are required to sleep under mosquito nets, and are warned against visiting native villages after dark. They are also given quinine in daily doses of 15 grains. The latter procedure is of distinct military value, but only because it delays the development of clinical symptoms while it is continued. As quinine does not kill sporozoïtes, it fails to prevent infection, and therefore it is not uncommon for many men to develop the clinical symptoms of malaria after they return to barracks and discontinue the drug. Obviously, an effective field prophylactic is urgently needed and for several years atabrine and other therapeutic agents have been tried experimentally, but so far with inconclusive results.

The great prevalence of malaria in Panama is well illustrated by an incident which occurred during maneuvers held recently near the Canal Zone border. As these maneuvers took place during the "dry season," it was decided to omit the use of quinine prophylaxis. Before the end of the second week, so many cases of malaria had developed that the continuation of the exercises was seriously interfered with.

Such occurrences show the importance of malaria as a military problem, and indicate the need for the development of more effective methods for the prevention of this disease in the field. The difficulties encountered by troops living under the relatively favorable peace time conditions which exist in the Canal Zone, afford a serious warning of the dangerous situation that would undoubtedly arise should it become necessary for our army to operate for a long period in the American tropics.

Equine Encephalomyelitis. Another mosquito-borne disease of some interest to our Army is equine encephalomyelitis. This is an epizoötic disease which occurs sporadically in various parts of the United States, and is caused by a filtrable virus, which may be identical with the virus of Borna disease. In 1933, Lieut. Col. Kelser,[18] at the Army Medical School, transmitted the virus to horses through *Aëdes ægypti*, and since that time several other species of Aëdes have been incriminated as potential vectors (Simmons, Reynolds and Cornell;[37] Merrill, Lacaillade and Ten Broeck;[23] Madsen and Knowlton[20]). The disease has not been common among army

animals but obviously it might occur at an inconvenient time and interfere with military movements.

The work of Kelser, moreover, is of considerable importance to human medicine as this was the first demonstration of the transmission of a purely neurotropic virus by mosquitoes. This fact naturally reopens the question as to whether certain acute infections of the central nervous system in man may also be carried by insects, and suggests many problems which still require investigation.

Conclusion. In this review, an attempt has been made to outline, briefly, the progress made in the Army's fight against some of the diseases caused by mosquitoes; also to point out certain weaknesses in the present lines of defense. The investigations of a host of civilian and military workers have armed us with information concerning the etiology of these diseases, and under favorable conditions we are able to prevent them by the tedious and costly method of eliminating their insect vectors.

Unfortunately, such methods of control cannot be applied effectively by an army actively engaged in the field, and we are still unable to protect adequately, troops operating in regions where these diseases are prevalent. To afford this protection, we must have effective, specific prophylactic agents, either drugs or vaccines. The search for such agents should be an important part of our Nation's preparedness program. This problem concerns not only the Medical Corps, but the whole medical profession, and it is hoped that eventually their combined efforts may lead to new victories in our War in the Air.

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A STATISTICAL STUDY OF ACUTE HEMORRHAGIC PANCREATITIS (HEMORRHAGIC NECROSIS OF PANCREAS).

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The belief that alcohol is in some way related to acute hemorrhagic pancreatitis has developed in this department from a review of the clinical story in fatal examples of this disease. This has been fortified by a not infrequent case with an explosive clinical course and striking postmortem findings. The following abstracts will illustrate:

Case Abstracts. Case 1.—A healthy American girl of 16, with no previous relevant history, in the course of an evening drank two moderately large glasses of Italian wine. Intoxication followed shortly thereafter but no other symptoms or signs were present. Shortly after going to bed at midnight, she vomited and experienced severe pain across the abdomen and back. The symptoms persisted until 4 A.M. when she is said to have fallen asleep. At 7 A.M. she was found dead.

Autopsy (No. 1685) disclosed numerous petechiæ in the gastric mucosa and an extraordinary pancreas. The duodenum, gall bladder and bile ducts showed no apparent lesions. The ampulla of Vater was patent. The pancreas was large, boggy and both externally and on cut section, revealed large, confluent dark red and purple-black patches between which

were still seen thin yellow-pink streaks of normal parenchyma. The tail of the pancreas was most involved and the head least. No abnormality of the pancreatic ducts was discovered. Microscopically, diffuse hemorrhage disrupted the tissue everywhere; the latter was necrotic—only the shadowy outline of cells remained. A few areas of intense leukocytic infiltration and fat necrosis were found, but by and large, cellular reaction was absent.

CASE 2.—A 30-year-old white male had both hands blown off in an explosion a year before his death. Physical recovery left him unhappy and he embarked upon a course of progressive alcoholism, so that shortly before his death he was consuming a quart of wine or whisky daily. On the day prior to admission he drank 2 quarts of sherry. Not long thereafter he began to vomit violently and experienced severe abdominal pain, especially in the epigastrium. The violence of the symptoms showed no abatement and he was sent to the hospital on the following day. On admission, he was critically ill and writhing in agony. There was a strong odor of alcohol on his breath. The abdomen was rigid and diffusely tender, most marked in the right upper quadrant. Immediate laparotomy revealed a hemorrhagic pancreatitis, with fat necrosis and peritonitis. A cholecystostomy was performed. The patient died less than 24 hours after admission.

Autopsy (No. 3873) showed a fatty liver, fibrino-purulent peritonitis and a pancreas similar in appearance to that described in Case 1. The body and tail were diffusely dark red. Microscopically, hemorrhage and necrosis predominated, although fat necrosis and leukocytic infiltration were occasionally prominent. In a few zones, proliferating young connective tissue suggested earlier insults of a similar type. No duct abnormalities were demonstrated.

In the light of such findings an analysis of the 4000 autopsies in our series was undertaken. Each anatomic diagnosis was reviewed and all protocols in any way related to pancreatic disease were abstracted, with especial emphasis on the clinical history (including alcoholism), the chief anatomic causes of death and also the postmortem condition of the stomach, pancreas, liver and gall bladder. All the available slides of liver and pancreas in these cases were reviewed. These cases were subdivided as defined below.

Acute Pancreatitis. All cases of hemorrhagic necrosis or acute pancreatitis not relevant to the present analysis were excluded. Those excluded were:

1. Associated with septicemia or systemic infection (scarlet fever, typhoid fever, tuberculosis, etc.).
2. Due to direct extension from a neighboring infection (peritonitis, retroperitoneal abscess, etc.).
3. Unequivocally related to severe passive congestion (usually associated with heart failure.).
4. Associated with widespread hemorrhagic tendency (purpura, leukemia, etc.).
5. Associated with carcinoma of the pancreas or neighboring structures.
6. The result of direct trauma to the pancreas (*e. g.*, bullet wound).

These lesions varied from pure hemorrhage to simple leukocytic invasion, and from tiny focal to extensive diffuse processes.

All instances not easily placed in the above categories were listed (Table 1). Of these, there were 38, or 0.95% of 4000 autopsies.

In 25, or 66% of the 38, alcohol was a probable factor. Only 6, or 15.8%, also has disease of the gall bladder. Although the duct systems were not examined with equal care in all instances, it is interesting that grossly observable obstruction to the pancreatic ducts was found only twice (Nos. 735 and 1117). In one (735) a stone at the ampulla of Vater produced a common channel between the common bile duct and pancreatic duct. In the other (1117), although a gall stone was present at the ampulla, there was some question in the mind of the operator whether a functioning common channel could have existed. No significant age distribution was noted. Thirty cases (79%) occurred in males. The pancreatic damage was often diffuse and the direct cause of death; often focal and apparently incidental to the cause of death. A direct but rough correlation existed between the time of death and the degree of inflammatory reaction; practically all of the instances with pure hemorrhage and necrosis occurred in patients who lived but a few hours. Several showed chronic inflammatory reaction or fibrosis in the pancreas. There was no demonstrable correlation between the amount of alcohol consumed and the degree of pancreatic involvement. In many of the protocols the stomach was noted to contain food. No. 2596 may be considered vascular in origin, but because of the prominence of the necrosis it was included in this series. The inclusion of No. 3577 may also be questioned. The patient was known to have long-standing hypertension and increasingly severe attacks of angina pectoris. During the course of an injection of 95% alcohol into the thoracic sympathetic ganglia he died rather suddenly after receiving a total of 6 cc. At autopsy, some acute congestion of the viscera was found, but nowhere, hemorrhage comparable to that in the pancreas.

Alcoholism. As a check on the high percentage of cases found associated with ingestion of alcohol, the attempt was made to ascertain the incidence of pancreatic disease in alcoholism. This was done in three ways.

1. *Acute Alcoholism.* The incidence of pancreatic lesions was studied in the group of patients who died during acute alcoholic episodes. The manner of death seemed unimportant, providing a reliable history, or more significantly, postmortem analysis indicated the presence of alcohol. In 4000 autopsies 51 such cases were found. Of these, 27, or about 53%, showed pancreatic lesions; 25 were acute and 2 chronic reactions.

In the course of reviewing these 51 cases the impression was gained but could not be substantiated that the rate of postmortem autolysis in the pancreas was considerably accelerated in instances of acute alcoholism.

2. *Chronic Alcoholism.* In 4000 autopsies there were 41 instances of chronic alcoholism. None of these at the time of death were under the influence of alcohol. Nineteen, or about 47%, showed pancreatic lesions, almost all of a chronic nature.

TABLE 1.—ACUTE HEMORRHAGIC NECROSIS OF PANCREAS (ACUTE PANCREATITIS).

Aut. No.	Age.	Sex.	Pancreas.						Alcohol.	Biliary tract.	Meta-plasia.	Other comment.
			Neer.	Hem.	Fat neer.	Ac. in-flam.	Fibro.	Foc. or diff.				
735	83	F	...	...	+	+	2+	Diff.	.....	Chr cholecystitis with stones	2+	Stone lodged in amp. of Vater with common channel. Acute cholangitis.
1057	60	M	±	...	...	±	...	Diff.	.....	Chr. cholecystitis with stones	...	Diabetic coma.
1117	68	F	4+	4+	4+	2+	...	Diff.	.....	Chr. cholecystitis with stones	...	Stone in common duct with ? obstr. in amp. of Vater. Chr. cholangitis. Common channel.
1149	46	F	3+	2+	3+	4+	2+	Diff.	"Prolonged alcoholic debauch recently"			
1501	51	M	+	+	...	...	...	Many focal	"Alcohol in stomach"	.....	...	Death followed much alcohol consumption.
1685	16	F	4+	4+	+	+	...	Diff.; mainly body and tail	"2 large glasses of Italian wine; intoxication"	.....	...	Death several hrs. after acute onset with vomiting.
1772	45	M	+	±	+	...	±	Focal	.....	.....	...	Moderate portal cirrhosis of liver.
1884	36	M	4+	4+	...	...	...	Diff.	"Intoxicated"	.....	...	Jailed for drunkenness, dead in morning. "Undigested food in stomach."
2025	53	F	2+	+	3+	+	+	Diff.	.....	Cholelithiasis		
2034	68	M	3+	3+	...	...	...	Focal	"Wine in stomach"	.....	...	Found dead.
2126	35	M	2+	4+	...	...	...	Diff.	.....	.....	...	Found dead. Small pieces of food in stomach.
2278	60	M	4+	4+	...	...	...	Diff.	"Drinking for 2 to 3 days"	.....	...	Found dead.
2380	55	M	?4+	3+	...	...	...	Diff.	"Drinking for 2 days"	.....	...	Died suddenly. Much undigested food in stomach.
2450	70	F	±	...	+	±	2+	Diff.	Chronic alcoholic	.....	2+	Marked portal cirrhosis of liver.
2469	40	M	±	4+	...	...	...	Diff.	"Odor of alcohol in stomach and viscera"	.....	...	"Alcoholic intoxication." Dead 15 mins. after arrival hosp.
2581	33	M	+	2+	...	...	...	Diff. in body and tail	"Very drunk"	.....	...	Much undigested food in stomach. Found dead.

2596	40	M	2+	4+	...	...	...	Diff. in tail and body	.....	.....	...	Syphilitic mesaortitis.
2896	52	M	?	±	...	...	...	Multiple focal	"Drunk"; 0.46% alcohol in brain	.....	...	Found dead. Stomach contained many food particles.
2920	45	M	?3+	3+	...	...	...	Focal	.....	.....	...	Found dead. Stomach filled with food. Fractured cervical vertebra from fall.
2922	27	M	4+	2+	+	...	...	Diff.	.....	.....	...	Much semisolid food in stomach.
2967	64	M	±	...	...	...	?	Focal	.....	.....	...	Portal cirrhosis of liver.
3007	50	M	±	3+	...	...	...	Diff.	Drinking rye before onset	.....	...	"Food débris in stomach."
3008	45	F	?4+	+	...	...	...	Diff.	0.17% alcohol in brain	.....	...	Found dead. Much semisolid food in stomach.
3021	64	M	4+	2+	3+	...	...	Diff.; mainly head	"Not a drinking man"	.....	...	Found dead.
3027	25	M	?2+	±	...	...	...	Multiple focal	0.4% alcohol in brain	.....	...	"Much recently ingested food in stomach."
3068	36	M	?4+	+	...	...	...	Diff.	0.45% alcohol in brain	.....	...	Much food in stomach.
3088	54	M	?4+	±	...	...	...	Diff.	0.37% alcohol in brain	.....	...	Many food particles in stomach.
3097	67	M	?4+	2+	...	...	...	Diff.	0.36% alcohol in brain	.....	...	Semisolid food in stomach.
3184	40	M	2+	...	3+	...	3+	Diff.	0.37% alcohol in brain; chr. alcoholic	.....	...	Pancreatic duct dilated but not obstructed.
3229	69	M	?2+	±	...	...	...	Focal	0.37% alcohol in brain; chr. alcoholic	.....	...	Found dead.
3290	45	M	?4+	±	...	...	...	Diff.	0.33% alcohol in brain	.....	...	Found dead
3304	43	M	...	+	...	...	±	Multiple focal	0.57% alcohol in brain	.....	...	Found dead
3308	45	M	4+	4+	...	...	...	Diff.	0.23% alcohol in brain	.....	...	Stomach "distended with partially digested food." Found dead.
3577	63	M	±	4+	...	...	...	Diff.	"Died during alcohol injection"	.....	...	Died suddenly 25 min. after beg. of alcohol inject. in thoracic ganglia for angina pectoris.
3812	43	F	4+	4+	4+	4+	...	Diff.	"Alcohol occasionally"	Chr. and acute cholecystitis with stones		
3817	50	M	?3+	+	...	...	...	Multiple focal	.....	.....	...	Fatty liver. Found dead.
3820	69	M	...	±	±	...	...	Focal	"Chronic alcoholic"	Cholelithiasis	+	Skull fracture with extradural clot. Found dead. Vomiting for several days.
3873	30	M	4+	4+	4+	2+	...	Diff.	"Heavy drinker of alcohol"	.....	...	Pain and vomiting—onset after drinking 2 qts. sherry.

3. *Cirrhosis of Liver.* In 4000 autopsies there occurred 51 instances of periportal cirrhosis of the liver. All examples of cirrhosis which were clearly biliary, toxic (*e. g.*, carbon tetrachloride), cardiac or associated with hemochromatosis were excluded. Of the 51 cases of the periportal variety, 25 (49%) showed pancreatic lesions. These also were practically all of a chronic nature.

The incidence of acute pancreatitis in the 4000 autopsies is about 1% (38 cases) and of chronic pancreatitis (or fibrosis of the pancreas) about 2.5% (97 cases). These results indicate an increase of 40 to 50 times in the incidence of pancreatic disease in the alcoholism group.

Further Relationships. No statistical analysis of hemorrhagic pancreatitis would be adequate without studying its relationship to the biliary tract. For despite many discrepancies, all observers are agreed in maintaining that hemorrhagic pancreatitis is associated in a high percentage with disease of the biliary tract. Figures vary considerably but reach as high as 60%.[5]

By the term "extrahepatic-biliary tract disease" is indicated not only acute or chronic inflammatory lesions, recognized grossly or microscopically, but also gall stones, with or without associated inflammatory change. Excluded are uncomplicated neoplasms. In the 4000 autopsies including all ages, there were 343 instances (8.6%) of extrahepatic-biliary tract disease. These figures are in agreement with most autopsy series, which find the incidence to be about 10% of all adults.

In the present series, extrahepatic biliary tract disease was found 6 times in the group of acute pancreatitis and 21 times in the chronic pancreatitis group,* an incidence of 15.8 and 21.7%, respectively. This is a significant rise in incidence as compared to the 8.6% in the 4000 autopsies. It agrees in substance if not in degree with other published data.

The other aspect of this problem, namely, the incidence of pancreatic lesions in biliary tract disease, has usually been neglected. The 6 cases of acute pancreatitis and the 21 cases of chronic pancreatitis were distributed through 343 cases of biliary tract disease, giving an incidence, respectively, of 1.8 and 6.1%. This is but slightly greater than their occurrence in the general autopsy series (1 and 2.4%, respectively).

The various writers who have stressed the frequent association of biliary tract disease with hemorrhagic pancreatitis have looked upon the former as primary, although they have been at a loss to explain the mechanism. In a small proportion of cases—less than 10%—the so-called "common channel" theory of Opie[9] has been

* All fibroses—interacinar, interlobular or focal—as well as chronic inflammatory reaction of the pancreas in adults are included in this term. This excludes the large number of chronic pancreatic lesions in congenital syphilis.

referred to. In this series of 38, as already mentioned, only 1 and possibly 2 cases—at most 5.3%—are thus explainable. In contrast, the following 3 cases are presented with a "common channel" but no pancreatitis.

CASE 3.—A 53-year-old negress with known hypertension died in the hospital with symptoms of cerebral involvement.

At *autopsy* (No. 1125) generalized arteriosclerosis with cerebral thrombosis and rheumatic heart disease with congestive failure explained her death. In addition, a thick-walled gall bladder filled with stones was found. We quote from the protocol. "It is thought advisable to open both the duct of Wirsung and the common bile duct from above downward. The duct of Wirsung . . . and the common bile duct . . . both open into a common ampulla. The common duct is not increased in size. It is filled with a green viscid bile. In this terminal dilatation (ampulla of Vater) just before it narrows into the orifice of the ampulla, a stone (5-sided, soft and pearly-white in color) is found jammed. It can be expressed through the opening in the common duct when pressed upon. It is the only stone found in the bile ducts." The pancreas was normal grossly and microscopically.

CASE 4.—A 48-year-old white female, because of frequent gall bladder colic, submitted to a cholecystectomy. The pathologic diagnosis was chronic cholecystitis with cholelithiasis. Following a short period of T-tube drainage of the common duct, convalescence progressed smoothly and bile appeared in her stools. During the next few months, however, several attacks of colic were experienced. Following the last attack she became jaundiced, had several chills and died shortly after admission to the hospital.

At *autopsy* (No. 2622) there was found an encapsulated accumulation of bile in the gall bladder bed with a fistulous communication to the common and hepatic ducts, a severe cholangeitis with liver abscesses, and a stone wedged firmly into the ampulla of Vater. The main pancreatic duct opened into the ampulla; the duct itself was neither stained nor otherwise remarkable. The common bile duct was thickened and dilated. A large accessory duct was found in the pancreas which opened separately into the duodenum 3 cm. distal to the ampulla. The pancreas was grossly normal; microscopically, there was an infiltration of neutrophils in the connective tissue of the head only.

CASE 5.—A 63-year-old white male with several attacks of gall bladder colic finally submitted to an operation. The gall bladder was distended. A cholecystduodenostomy was performed but the patient died several days later.

At *autopsy* (No. 1842) there was found a chronic and acute cholecystitis and cholelithiasis, dilatation of the common, hepatic and pancreatic ducts which opened into a common ampulla and rupture of the anastomosis between the gall bladder and duodenum, with peritonitis. No stone was found at the ampulla of Vater, although it was dilated to 1.5 cm. in diameter. The pancreas was grossly negative and microscopically showed a few perivascular lymphocytes.

Another factor recently brought into the limelight[12] in the pathogenesis of acute pancreatitis has been the metaplasia of the pancreatic duct epithelium. The general occurrence and anatomic features have been described in detail by Priesel[11] and Baló and Ballon.[3] Rich[12] has directed attention to duct obstruction in the

causation of acute pancreatitis and has ascribed to these metaplastic nodules the rôle of obstructing agent in a high percentage of these cases.

In the course of the present review, attention was especially directed toward the state of the duct epithelium. The slides of 261 pancreases were examined. These included 84 normal pancreases, 63 with some form of acute reaction and 114 with fibrosis or chronic reaction. Included among these chronic forms were instances of congenital syphilis. A total of 32 cases with metaplasia of the duct epithelium were found. Three of these occurred in the group of acute pancreatitis (Table 1), 5 were in normal pancreases and 24 in pancreases showing fibrosis or chronic pancreatitis.

Comment. The rôle of alcohol in the causation of acute pancreatitis is by no means clear. Only sporadic cases are sufficiently dramatic to attract attention to the alcohol. The majority show pancreatic involvement of an essentially minor nature—and are therefore easily overlooked. In addition, the wide use of alcohol probably has contributed to the neglect of its rôle as a causative factor.

Isolated reports have appeared from time to time in the literature. For instance, in 1907 Egdahl[6] analyzed 105 cases of acute pancreatitis. His largest number (42%) was associated with gall bladder disease; the next in infrequency consisted of 32 cases following gastro-duodenitis, of which 17 were associated with alcohol. In 1934, Myers and Keefer[8] analyzed 29 cases of pancreatic necrosis, 22 of chronic pancreatitis and 24 of focal fat necrosis and, respectively, found 12, 7 and 9 associated with either cirrhosis of the liver, fatty liver or acute and chronic alcoholism, that is approximately one-third. Isolated case reports have also been published. That of Adams and Bouloux[1] is representative. They recorded a boy aged 20 who collapsed after drinking rum and died in 20 minutes. At autopsy, the sole pathologic lesion was fresh hemorrhage in the pancreas. Several others drinking the same rum were unaffected.

How does alcohol act? Egdahl[6] assumed that it was merely the cause of the gastro-duodenitis which in turn caused the pancreatitis. Myers and Keefer[8] discussed several theories: 1, that alcohol in the blood damages the pancreas directly; 2, that duodenal congestion obstructs or infects the ducts; 3, that persistent vomiting causes regurgitation of duodenal contents into the ducts. Rich[12], on the basis of Gizelt's work,[7] believed that alcohol like food stimulated pancreatic secretion and that the pancreatitis resulted from rupture of acini whose excretory ducts were blocked by metaplastic epithelium.

No theory of the pathogenesis of acute pancreatitis is offered in this communication. Attention, however, is directed to a few facts. The presence or absence, the severity or rate of progress of the pan-

creatic lesion does not appear to vary with the quantity of alcohol ingested.

Apparently, it may attack an individual who has had little or no previous indulgence (Case 1), while it may completely spare a chronic and severe alcoholic. Alcohol alone is not enough.

Several other sets of data, detailed above, deserve comment.

The high incidence of biliary disease with pancreatitis is accepted by many and yet without presenting the reverse of this relationship, most writers have assumed that biliary disease causes pancreatitis. It is desirable therefore again to repeat what the data included in this communication show: *that the incidence of gall bladder disease is significantly increased in pancreatitis but the incidence of pancreatitis in gall bladder disease is only slightly (if at all) higher than in the general autopsy series.* This is doubly interesting because in recent years several investigators[4,10,14] have been revising the interpretation of the "common channel" concept. The finding of pancreatic enzymes in the gall bladder has led them to postulate a pancreatic reflux, and a few[4,14] have ascribed to this mechanism an important rôle in the causation of cholecystitis. Popper,[10] who does not believe the evidence for such causation sufficient, has published, however, a series of figures which bear mention. He removed bile sterilely at operation in 219 instances—210 direct from the gall bladder and 9 from the choledochus. In 37 (17%) he demonstrated the presence of pancreatic ferments; several were from bacteriologically and microscopically normal gall bladders. In 18 cases of acute hemorrhagic pancreatitis in which he examined the bile, ferments were found in 16 (88%).

The simplest interpretation of Popper's results is that in acute pancreatitis there is an obstruction to the outflow of pancreatic secretion, which takes the path of least resistance, when a "common channel" is present. This explanation assumes that obstruction is all-important in the pathogenesis of this disease; and, as Rich[12] has shown, the rupture of the acini with escape of the enzymes into the surrounding tissue initiates the pathologic processes. Other experimental work[13] is also in agreement with this. The instances in which the classical mechanism first described by Opie[9] operates, may be explained similarly, *i. e.*, by obstruction to the outflow of pancreatic secretion. All experimenters who have produced pancreatitis experimentally by the injection of bile into the pancreatic ducts, have injected the material under pressure, or else used infected bile. Archibald[2] injected sterile bile into the pancreatic ducts of cats and was able to produce only a relatively transient edema. Cases 3, 4 and 5 which are abstracted above, show at least that a stone impacted in the ampulla of Vater with a resultant "common channel" is not necessarily followed by pancreatitis.

The mechanism of obstruction to the pancreatic ducts is by no

means clear. In a few instances an impacted stone at the ampulla, a tumor or other extrinsic masses pressing on the pancreatic duct may be operative. In our own series, anatomic obstruction was not found more than a few times, although dilated pancreatic ducts were not infrequent, especially in a few cases of chronic pancreatitis. Archibald's[2] explanation of either edema of the papilla of Vater or a spasm of the sphincter of Oddi, although based on animal experimentation has never been proved in human cases.

In what percentage of acute pancreatitis obstruction is operative, and what other factors are involved must for the present remain unanswered. No one can fail to be impressed by the complexity and multiplicity of factors involved in this disease.

Summary. 1. A review of 4000 necropsies at the New Haven Hospital revealed 38 (1%) with acute hemorrhagic pancreatitis and 97 (2.4%) with chronic pancreatitis.

2. In 25 (66%) of the acute cases, alcohol was an associated factor. In 6 (15.8%) disease of the extrahepatic biliary tract was present.

3. In 51 instances of individuals dying during acute alcoholic episodes, 27 (53%) showed pancreatic lesions (25 acute and 2 chronic).

4. In 41 instances of chronic alcoholism, 19 (47%) showed pancreatic lesions, all of a chronic nature.

5. In 51 instances of periportal cirrhosis, 25 (49%) had pancreatic lesions.

6. In 343 cases of extrahepatic biliary tract disease, there were 6 instances of acute pancreatitis and 21 of chronic pancreatitis, an incidence of 1.8 and 6.1%, respectively.

7. The present material shows that the incidence of gall bladder disease is significantly increased in pancreatitis; but the incidence of pancreatitis in gall bladder disease is only slightly (if at all) higher than in the general autopsy series. While the data offer no relation to the pathogenesis of acute pancreatitis, they indicate at least the complexity of the problem.

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THE NATURE AND THE MECHANISM OF STAINING OF THE ERYTHROCYTIC RETICULUM.

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It is generally accepted, especially since the exhaustive experiments of Key,[1] that the reticulum of young erythrocytes is not a preëxisting structure, but the pattern formed by the action of the vital stains on the basophilic substance of the "polychromatophilic" cell, while the cell is still wet. This pattern and the site it occupies within the cell varies with the different dyes; however, in its general appearance it is always characteristic of the particular stain. Because brilliant cresyl blue acts more uniformly and much faster than any of the others, it is now the most common vital stain used for the demonstration of the reticulum in the routine laboratory technique. Inasmuch as the colors of the brilliant cresyl blue and of the methylene blue are indistinguishable, one might believe that the reticulum continues to retain the color of the brilliant cresyl blue stain after counterstaining. Invariably, however, specimens stained with the brilliant cresyl blue alone and kept either uncovered or mounted with Canada balsam, lose their stain within a short time, while the counterstained specimens usually preserve the stained reticulum almost indefinitely. Still, at times, a few counterstained preparations, when examined at a later date, are found to be void of the reticulum or show the same in a faded state without any apparent staining disturbance of the basophilic structure of the white blood cells, while other preparations, made simultaneously and at times mounted on the same slide, continue to show the reticulum brilliantly stained. To explain the cause of this discrepancy, and at the same time to investigate further the nature of the basophilic substance, especially as to its staining mechanisms, is the purpose of this paper.

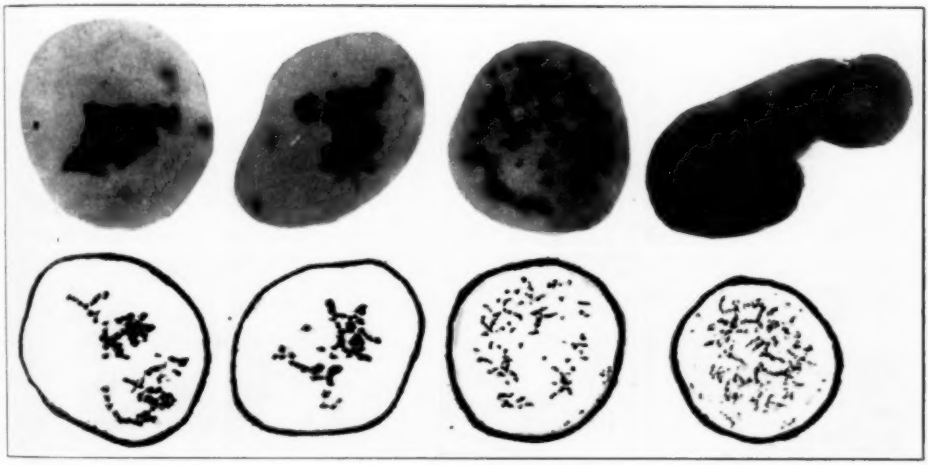
Blood specimens from patients with pernicious anemia in induced and spontaneous remission, sickle-cell anemia and anemia of hemorrhage, showing a reticulocyte count of over 20%, were used. After gentle defibrination, small amounts of cells were placed in centrifuge tubes and stained by mixing with an almost equal amount of solutions of various stains in 0.85% of sodium chloride. After it had been established, by proper wet and dry preparations, that the reticulum was well stained, the dye was removed by repeated washings with 0.85% solution of sodium chloride. After the last centrifugation the excess sodium chloride solution was discarded and wet and dry preparations were examined to ascertain that the cells showed no trace of the stain, *i. e.*, no trace of a demonstrable reticu-

lum. Films from such specimens were then stained with the Wright's stain in the usual manner. It was then observed that the cells showed a reticulum brilliantly stained blue, in a percentage corresponding to the known reticulocyte percentage of the fresh specimen. The reticulum always appeared blue, regardless of the color of the vital dye originally used (*e. g.*, neutral red) and without any demonstrable difference from a fresh specimen in pattern or brilliance. The pattern remained characteristic of the vital stain used and corresponded to the known pattern for that particular stain.

Similar experiments were then carried out on slides. Blood films, stained with vital stains of different colors, such as brilliant cresyl blue and neutral red, were fixed with methyl alcohol and then flooded with water. This process removed all trace of the vital stain. After drying, the slides were stained with Wright's stain in the usual manner. The reticulum reappeared on these slides always brilliantly blue, regardless of the color of the vital stain, and always assumed the characteristic pattern of the particular dye.

These results were more simply, but even more clearly, illustrated when, in place of counterstaining with the Wright's stain, another vital dye of a different color than the first was used. The vitally stained blood films were fixed with methyl alcohol, flooded with water sufficiently to remove the vital stain, and dried in the air. A drop of a solution of a vital stain of a different color than the one used at first was then placed on a cover slip, and this inverted and deposited over the slide. The reticulum then reappeared showing the pattern of the first stain but in the color of the second. If, for example, brilliant cresyl blue was first used and then neutral red, the reticulum appeared red but in the characteristic pattern of the brilliant cresyl blue. If the stains were used in the reverse order, the reticulum appeared blue but had the neutral red pattern.

Discussion. These experiments seem further to confirm the theory that the reticulum-forming material is a structureless, protoplasmic substance, evenly distributed in the stroma of the young erythrocyte, decreasing as the cell matures. Methyl alcohol, or similar fixative agents, causes a uniform precipitation of this substance, which takes basic stains. The uniform bluish staining of the stroma of such cells presupposes such a condition. The intensity of staining depends upon the amount of the basophilic substance present. The introduction of the so-called vital stain in the wet preparation causes a flaky precipitate. The shape and size of these flakes, as well as their arrangement within the cell, differ with the different vital stains used. These flakes, the "reticulum," are not permanently stained with the vital stain (the brilliant cresyl blue, for instance, in the routine blood technique) but such stain is dissolved and washed off during the process of counterstaining. Then the reticulum is restained with the methylene blue of the counter-



1 2 3 4

FIG. 1.—Forms of reticulum in red blood cells. The upper row shows photographs and the lower row camera lucida drawings of red blood cells stained as follows: (1) Neutral red. (2) Neutral red, washed, then Wright's stain. The red color is replaced by blue. (3) Methylene blue. (4) Brilliant cresyl blue. The amount of reticulum substance is greater in the more immature cells than in the older forms, and the sparse granules of the older forms are much the same with any of the stains. With brilliant cresyl blue the fine granules tend to form filaments. With methylene blue the filaments are finer and shorter. With neutral red the granules are coarser, and clumping is common.

staining material, more, as it seems, permanently. The permanency of such staining then seems to depend upon the more or less complete removal of the brilliant cresyl blue. When small amounts of the counterstaining material are used, and then the preparation is not flooded with water for the purpose of differentiation, but, instead, only a few drops of water are used, apparently most or some of the brilliant cresyl blue is retained which later fades out, causing the reticulum to "disappear." If such preparations are then restained with the Wright's stain, the reticulum reappears as bright and as brilliant as is shown on the fresh preparations. For this reason, it seems that, during the counterstaining process, an excess of stain and an excess of water, as much as the slide or cover slip will hold, should be used to make sure that the brilliant cresyl blue is redissolved and completely replaced by the more stable methylene blue.

Summary. 1. Reticulum in immature erythrocytes is a precipitate caused by the interaction between a basophilic substance in the cell and the vital dye.

2. In counterstaining the reticulocytes with Wright's stain, the reticulum stain is replaced by methylene blue.

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ACUTE HEMOLYTIC ANEMIA.

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Two cases of acute hemolytic anemia of the Lederer[9] type form the basis of this report. The first closely resembles the other 55 cases thus far reported; the second is unusual in that autoagglutination of the patient's blood was observed. As far as I know, this phenomenon, rare in itself, has been seen only twice before in cases of acute hemolytic anemia (Giordano and Blum[5]; Patterson and Smith[14]).

Case Abstracts. Case 1.—E. T., a female aged 6, was first seen on January 23, 1934, because of vomiting, fever and jaundice. On January 19 the child felt chilly, had an elevation of temperature to 101° F., and complained of headache. Vomiting began the following day and was persistent and profuse. The mother also noticed at this time that the child was jaundiced and that the urine looked bloody. The symptoms were more pronounced when I saw the patient on January 23. At this time there was intense jaundice, severe pallor, restlessness, and dehydration. The spleen and liver could not be felt. The urine looked bloody, but did not have the coffee-ground appearance that it has in hemorrhagic nephritis;

subsequent examinations of the urine showed no red cells but the presence of large amounts of hemoglobin. A diagnosis of acute hemolytic anemia was made and hospitalization advised.

The child was admitted to this hospital on the same day and was immediately given 300 cc. of Type I blood by direct transfusion from the father. A few hours after the transfusion definite improvement was seen. Examination of the blood before transfusion showed the following: Many reticulocytes, anisocytosis and poikilocytosis; red blood cells, 800,000; white blood cells, 12,900 with 85% neutrophils, 13% lymphocytes, and 2% eosinophils; and platelets, 300,000. The hemoglobin was 20% (Sahli). Fragility of the red cells was normal; hemolysis began at 0.425 and was complete at 0.250. The test for fragility was repeated later and found to be essentially the same, 0.425 to 0.275. The Donath-Landsteiner test was negative. Blood cultures taken on the 23d and 25th of January were negative. The blood contained 114 mg. % sugar, 61 mg. % urea, 1.8 mg. % creatinine, 138 mg. % cholesterol, 11.3 mg. % calcium, 3.02 mg. % inorganic phosphorus, and 1.05 mg. % bilirubin. The total non-protein nitrogen was high, 111 mg. %. The indirect Van den Bergh reaction was ++. The urine contained hemoglobin and large amounts of albumin. The temperature remained elevated (101° to 102.2° F.) for 2 days and then subsided. For other blood examinations see Chart 1.

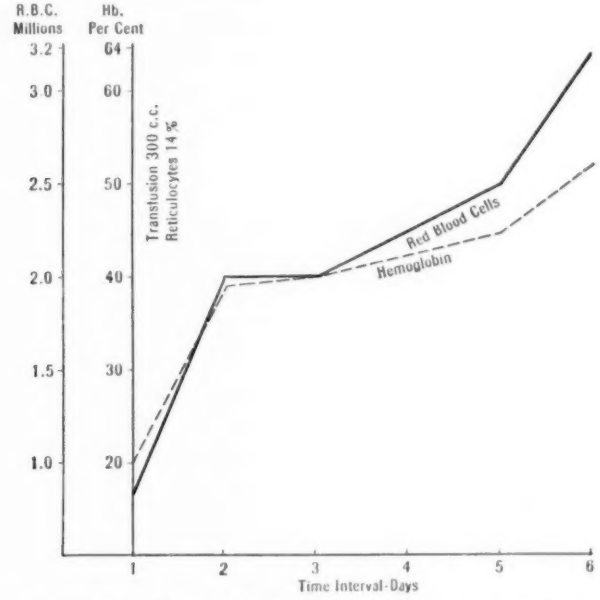

CHART 1.—Case 1. Hemoglobin content and red blood count before and after transfusion.

The anisocytosis and the poikilocytosis persisted for several days; the reticulocytes disappeared within 48 hours after the transfusion. The child was discharged 6 days after admission to the hospital.

CASE 2.—J. H., a female aged 5, was first seen on December 24, 1936, because of headache, jaundice, pallor, and bloody urine. The parents stated that the child had a sudden rise in temperature to 103° F. 3 days before and at the same time vomited and complained of severe abdominal

pain. The following day severe pallor and jaundice were observed; at this time, too, the urine was bloody. The family physician said that intense restlessness had been present from the beginning and had been uninfluenced by large doses of phenobarbital.

Physical examination revealed an acutely sick child with extreme pallor and frank jaundice; the mucous membranes of the mouth were dry. The sensorium was cloudy. The liver and spleen could not be palpated. A loud systolic murmur was heard at the third intercostal space at the left sternal border. The temperature was 104° F. A diagnosis of acute hemolytic anemia was made and hospitalization was advised.

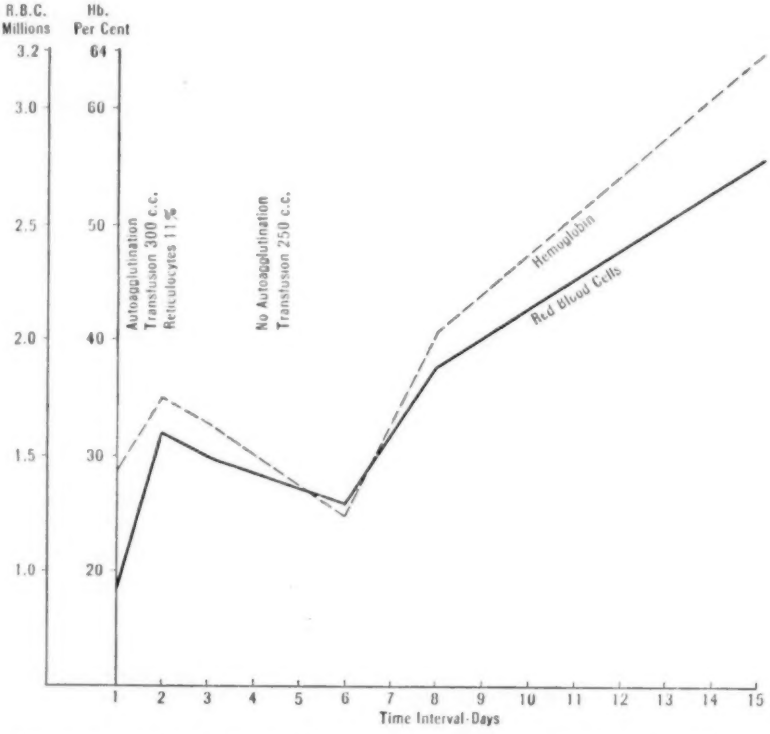

CHART 2.—Case 2. Hemoglobin content and red blood count before and after transfusion.

On admission to the hospital arrangements for an immediate transfusion were made. Delay was encountered because of the presence of autoagglutination of the patient's blood. The patient's blood clumped when placed on a slide, without the addition of typing sera as well as with the addition of typing sera; thus it was impossible to type the child's blood. The child's condition was becoming more grave and in desperation we decided to use the father, who fortunately was a universal donor. Three hundred centimeters of blood were given slowly by the indirect method, with no reaction. Five days later the autoagglutination was no longer present and it was determined that the child's blood belonged to Group 2. Subsequent examinations of the blood failed to show autohemagglutination. Immediate improvement followed the transfusion; the color improved, the somnolence

disappeared, the vomiting stopped and the child no longer complained of abdominal pain. The temperature ranged from 101° to 102° F. for 4 days and then subsided. On the fourth day of the child's stay in the hospital the spleen could be felt one-half finger's breadth below the costal margin.

Examination of the blood on admission before transfusion showed 890,000 red blood cells, 13,800 white blood cells and 29% hemoglobin content (Sahli); many reticulocytes, poikilocytosis and anisocytosis, and a marked shift to the left in the white cells were observed. The fragility test was normal (0.475 to 0.350). The urine contained 3+ albumin, a large amount of hemoglobin, a considerable amount of urobilin but no red cells. The chemistry of the blood was as follows: sugar, 146 mg. %; cholesterol, 240 mg. %; urea nitrogen, 16.8 mg. %; uric acid, 3.8 mg. %; creatinine, 1.4 mg. %. In this case no non-protein nitrogen retention could be demonstrated; subsequent examinations of the blood also failed to show any retention. The icteric index was 21.5 units and the indirect Van den Bergh reaction was positive. Cultures of the blood were consistently negative. On the fifth day after admission, because of the slow improvement in the blood, another transfusion of 250 cc. of whole blood from the father was given; this was followed by rapid improvement (Chart 2).

There was a gradual decrease in the icteric index and on January 6 the indirect Van den Bergh reaction was no longer positive.

On December 25, 2 days after the first transfusion, a hematocrit study showed a normocytic hyperchromic anemia: red blood cells, 1,600,000; hemoglobin, 6 gm. per 100 cc. of blood; color index, 1.09; volume index, 1.06; saturation index, 1; mean corpuscular volume, 87; mean corpuscular hemoglobin, 37.4 micromicrograms, and the mean hemoglobin concentration, 44%. Chart 2 shows the changes in some of the blood elements following the first and second transfusions.

The child was discharged from the hospital as well on January 8, 1937. Subsequent examinations did not show any abnormal physical or hematologic findings.

Discussion. Acute hemolytic anemia, with or without hemoglobinuria, may result from a variety of infections, poisons (fava bean), or drugs (sulphanilamide). Thus Bartonella infection is an example of a blood infection which produces an acute severe hemolytic anemia with or without hemoglobinuria; here the red cells are invaded by the organisms and broken up. The acute hemolytic anemia of Lederer is a disease of unknown etiology and is characterized by a sudden onset with elevation of temperature, severe anemia, icterus, leukocytosis and, at times, hemoglobinuria.

The age incidence varies from 5 months to 35 years. Parsons and Hawksley[13] reported 6 cases under 2 years of age and Lederer,[9] 2 under 2 years. In infants, the clinical course is more rapid, the anemia develops with greater speed and is more severe than in adults.

The Clinical Picture. The onset is sudden and occurs with fever which may range from 99° to 105° F.; diarrhea, vomiting, abdominal pain, severe headache, and marked restlessness are outstanding symptoms. In 24 to 48 hours and sometimes longer, weakness, marked pallor, and definite jaundice develop. The liver and spleen sometimes become enlarged at this stage. From observations on my cases and from a study of the cases reported, it is my impression

that there are two distinct phases in the symptomatology of this disease. In the first phase, which lasts from 24 to 72 hours or longer, the symptoms resemble closely those seen in any severe infectious disease; from the appearance of the patient and even from careful hematologic studies it is impossible even to suspect that a serious blood crisis is impending. In the second phase, the hematologic crisis dominates the picture; *i. e.*, the marked pallor, the severe jaundice, the rapid and sharp drop in the red cells and in hemoglobin content of the blood completely obscure the previous train of symptoms. Thus, in 3 cases observed from the beginning of the disease it was noticed that a drop in red cells from 4,500,000 to 600,000 to 800,000 occurred within a few hours. As a rule, the temperature lasts from 4 to 5 days.

The restlessness observed early in the disease is not due to air hunger since it is present when the hemoglobin content and red cell count are still fairly high. Later the restlessness is due, without doubt, to the anoxemia which results from the severe anemia. Hemoglobinuria was seen only once in 9 cases by Parsons and Hawksley,[13] twice in 6 cases by Lederer,[9] once in 1 case by Patterson and Smith,[14] twice in 2 cases by Giordano and Blum,[5] and twice in 2 cases by the author. It seems that hemoglobinuria is encountered in the severe cases and probably results from the sudden hemolysis of a large number of red cells. Hemic murmurs are frequently noted and are usually systolic in time. In 1 case, however, diastolic murmurs at the base have been described.[11] These murmurs, whether systolic or diastolic, disappear on recovery from the anemia; my second patient had a loud systolic murmur which subsequently disappeared. It is the consensus of opinion that these murmurs are temporary and more or less harmless. It is believed by some, however, that Moschcowitz's[12] case is an instance of this disease in which organic cardiac changes were found. Moschcowitz reported the case of a patient who had a severe hemolytic anemia which proved to be fatal. Necropsy showed hypertrophy of the left ventricle of the heart; microscopically, every field revealed from 1 to 12 thrombi in the terminal arterioles or capillaries. Careful study of his case, however, shows no resemblance to the disease described in this communication except for the severe anemia. For example, his case showed a marked increase in the fragility of the red cells, petechiæ, and hemiparesis, manifestations not observed by any other author. Retinal hemorrhages have been reported by Holst[6] and by Lederer[9] and are more characteristic of the disease in adults than in children. Blood cultures have been negative in the cases thus far reported.

Hematology. The red cell count varies from 600,000 to 1,500,000 to 2,000,000 and the hemoglobin content from 10 to 40%; anisocytosis and polychromasia are always present; occasionally, poikilocytosis is also observed. The color index is about unity or above;

reticulocytes and erythroblasts are found in large numbers; macrocytes, basophilic stipling and megaloblasts are also seen—all evidence of a vigorous attempt on the part of the bone marrow to repair the anemia.

The fragility of the red cells, the bleeding and coagulation time, and the platelet count are normal. When hemolysis is rapid and severe, an increase in the number of white cells with many young cells is found. The number of white cells may be as low as 3000[15] or as high as 80,000;[5,9] thus it is evident that the disease can be confused with leukemia.

Generally, the blood picture is that of a hyperchromic megalocytic anemia; this, together with the marked increase in reticulocytes, is characteristic of a profound anemia with hyperfunction of the bone marrow. The second case described in this communication, however, showed a normocytic hyperchromic anemia; the myeloblasts, too, were not as numerous as in some of the cases reported by other observers.

The indirect Van den Bergh is positive, the icteric index is high (20 to 90 units) and urobilinogen is found in the urine. As a rule, there is a marked non-protein nitrogen retention; it was present in 1 of the cases reported here; the urea nitrogen was 61 mg. % in 1 case but only 16.8 mg. % in the other. In 1 case reported by Lederer[9] the urea nitrogen ranged from 59 to 98. In all cases normal values are found after recovery is well established. Whether this increase is due to a temporary renal insufficiency, as Lederer believed, or whether it is due to the accumulation of protein products resulting from the marked increase in blood destruction it is difficult to say. Because of the rapid return of these values to normal after transfusion it is logical to believe that the latter view is the correct one.

Etiology. No definite etiologic factor has been found thus far, and all attempts to determine the cause of this disease have been unsuccessful. The sudden onset with fever suggests that the disease results from some infection, but thus far no definite infectious process has been demonstrated; this was true in the 2 cases observed by the author. Repeated blood cultures were negative and repeated physical examinations failed to show any evidence of infection. Witts,[18] however, states that the disease may be ushered in with sore throat and influenzoid symptoms. It is possible and even likely that no single etiologic factor is responsible for the disease.

Lederer believed that the exciting factor, probably infectious in nature, acts as an irritating stimulus on the reticulo-endothelial system with consequent increase in the blood destruction.

From a study of the course of this disease and its hematologic picture, it seems that there are two possibilities for consideration as far as pathogenesis is concerned; first, that there is produced in this disease during its primary phase some hemolytic agent which

rapidly breaks up a large number of red cells and that the large number of myeloblasts, erythroblasts and reticulocytes found in the blood results from a strong effort on the part of the bone-marrow to make good the sudden deficiency; and, second, that the cells are rendered more fragile and break up rapidly even in the absence of any new hemolyzing agent because some toxic substance is produced which acts on the bone marrow to prevent the production of normal and properly functioning erythrons. The author believes that the first view is the correct one for the following reasons:

1. The bone marrow apparently is able to respond to the tremendous demands made upon it, as judged by the large number of reticulocytes and erythroblasts in the blood: 67% reticulocytes have been reported in 1 case by Fiessinger, Decourt and Lour[4] and 43% in another by Patterson and Smith.[14]

2. Recovery is complete and takes place in a comparatively short time in every typical case; this is not true of other blood dyscrasias in which the bone marrow is at fault.

3. In no disease in which the bone marrow is depressed or disturbed in its function does the dramatic response follow transfusion as it does in acute hemolytic anemia; only a true substitution therapy will produce an effect comparable to this one. Thus, it is the author's belief that, when a transfusion is given, antihemolytic agents are introduced in sufficient numbers to prevent further excessive hemolysis.

The rôle of hemautoagglutination in the etiology of this disease is not clear. Hemautoagglutination is a clumping of erythrocytes into irregular masses visible to the naked eye and occurring in the presence of the individual's own serum at room temperature and reversible at body temperature.

In autoagglutination there is a definite interaction of agglutinin in the serum with the agglutinogen in the red cells; however, the union can occur only at a temperature below that of the body. It is important, therefore, in collecting blood for examination, that the vessel be warm and kept warm by placing it in a water bath at 39° C.; when typing smears, warm slides should be used. Had these precautions been taken in Case 2 we would have had no difficulty in matching the child's blood. Only about 25 true cases of autoagglutination have been thus far reported. This phenomenon has been observed in pernicious anemia and other severe anemias, in acholuric jaundice with marked enlargement of the spleen, in a case of multiple myelomas with hyperproteinemia, and paroxysmal hemoglobinuria, in severe pneumonias and in staphylococcus septicemia.[1,7,16,17] It has been observed in only 3 cases of acute hemolytic anemia. The first case was reported by Patterson and Smith[14] in 1936, the second by Giordano and Blum[5] in 1937, the third case is reported in this communication. The autoagglutination persisted for 21 days in Giordano and Blum's case, for several weeks

in Patterson and Smith's case, and for 5 days in the author's case. It is doubtful whether this phenomenon is responsible for the acute hemolytic process in this disease; it is more likely that the auto-agglutination is a phenomenon which appears during the height of the disease as it does in other severe anemias, and disappears on recovery. It is even problematic if it ever enhances hemolysis; for example, it was present for 21 days in Giordano and Blum's case, yet improvement after one transfusion was striking and continued. No apprehension need be felt as to any ill effects from transfusion provided the blood of the patient and that of the donor are properly matched and cross-matched. It is advisable, however, to use the indirect method, to make sure that the donor's blood is kept at body temperature; it is also suggested that the patient be placed under some heating apparatus. It is unnecessary and at times even undesirable to begin the transfusion with extremely small amounts of blood. None of the 3 patients showed any ill effects from the transfusions although fairly large amounts of blood were injected; three transfusions of 300 to 500 cc. each were given. Giordano and Blum's patient had a mild immediate reaction but his temperature dropped and the general condition improved within a short time.

Differential Diagnosis. In children, the disease may be confused with acute leukemia and with acholuric jaundice, particularly if the patient is seen during a crisis. The confusion with leukemia occurs because of the vigorous response of the bone marrow to the sudden increased hemolysis, with the result that large numbers of immature white as well as red cells are sent out into the circulation. When the total count is high, as it is in some cases, the mistake is even more likely to occur. The therapeutic test, however, should unequivocally determine the diagnosis. In acute hemolytic anemia, the response to transfusion is dramatic, whereas in leukemia the patient is certainly not benefited and, at times, his condition is even aggravated by the procedure. The differential diagnosis from acholuric jaundice is at times extremely difficult because in both conditions fever, severe abdominal pain and intense jaundice may be present at the onset. There is a considerable number of cases of acholuric jaundice which go unrecognized until a crisis occurs. The outstanding differentiating characteristics are the family history, the increased fragility, the microcytosis, the absence of hemoglobinuria, and the enlarged spleen in acholuric jaundice. Large numbers of reticulocytes are found in both diseases. The spleen may be enlarged in acute hemolytic anemia, but the increase in size is rarely present before the third or fourth day of the disease; moreover, the spleen never attains the size observed in acholuric jaundice. The differentiation may become very difficult if the microcytosis and the increased fragility are absent in acholuric jaundice, as occurs in 10 to 15% of the cases.[2] It is suggested that, if acholuric jaundice

is suspected and microcytosis and increased fragility are absent, other members of the family be examined for these changes. The differentiation between acholuric jaundice and acute hemolytic anemia is of more than academic significance, particularly in the light of the results shown by Doan in his recent work in acholuric jaundice. Doan and his co-workers[3] advise splenectomy during a crisis and have reported excellent results with this procedure. Transfusion, while it acts as a specific in acute hemolytic anemia, is of little benefit and perhaps even harmful when given during a crisis to a patient suffering from acholuric jaundice. Obviously, splenectomy, performed on a patient suffering from acute hemolytic anemia of the Lederer type, would be calamitous.

The prognosis is good provided the diagnosis is made early; recovery rapidly ensues upon the institution of proper treatment which consists of transfusion. Usually one transfusion is sufficient, although occasionally more than one may be necessary. The response to transfusion is remarkable and appears to act as a specific. A transfusion should be given as soon as the diagnosis is made, or even if the disease is suspected. It miraculously changes in a few hours the clinical picture of an alarmingly ill patient who seems about to die to that of one on the road to recovery.

How the transfusion acts is a moot question. It is believed by some that the beneficial effect may be due to the fact that some deficiency factor is supplied, thus aiding in the production of normal red cells.[5] It is more likely, however, that the transfusion achieves its remarkable results, first, by supplying an antilytic agent; this is undoubtedly its most important effect; second, by sparing a very much overworked bone marrow and not by stimulating it as Kuhl,[8] Manfredini,[10] and Giordano and Blum[5] believe. As evidence of this there is the marked reduction in the number of reticulocytes which practically always follows a single transfusion. In Patterson and Smith's[14] case the number of reticulocytes was 43% before transfusion; after transfusion there was a gradual decline to 2%; third, by relieving the anoxemia and by tiding the patient over a critical period.

Summary. 1. Two cases of acute hemolytic anemia of the Lederer type are described; in 1 case the unusual phenomenon of hemautoagglutination was observed.

2. Clinically, there are two phases in this disease. The first phase is characterized by fever, vomiting, abdominal pain, somnolence and restlessness; there is nothing to distinguish the disease in this stage from the initial stage of any other severe infectious disease. The second phase is characterized by a sudden severe hemolytic crisis which results in frank jaundice and in a severe anemia of the hyperchromic megalocytic type.

3. The hemautoagglutination is not responsible for the hemolysis but may interfere with the proper examination and typing of the blood unless special precautions are taken.

4. It is suggested that the disease is due to the introduction or evolution of some hemolytic substance which rapidly destroys large numbers of red cells; the opinion is also advanced that the bone marrow is neither depressed nor primarily at fault but that, on the contrary, the bone marrow makes a vigorous effort to correct the sudden anemia; this is evidenced by the large numbers of reticulocytes, nucleated red cells, and young white cells seen in the blood.

5. Most characteristic is the immediate improvement which follows one transfusion; the theory is advanced that some antilytic agent is introduced with the transfused blood and is responsible for the complete arrest of the hemolytic process.

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OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

V. The Etiologic Relationship Between Water Retention and Arterial Hypertension.*†

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In the preceding papers of this series[3a-f] it has been demonstrated that, in the absence of severe anemia, heart disease and acute nephritis, water retention in pregnancy is conditioned primarily by the level of the plasma proteins, and may be altered, just as in non-pregnant individuals, by changing the intake of electrolytes. It

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has also been shown that, coincident with the induction of marked water retention by the administration of sodium salts in pregnant women with hypoproteinemia, the arterial blood pressure rises and symptoms of preëclampsia may appear.[3c,d] The observations recorded in this paper indicate that the arterial blood pressure falls and symptoms of preëclampsia disappear coincident with the loss of retained water induced by decreasing the amount of sodium in the diet[3f] of pregnant women with hypoproteinemia and hypertension arising during pregnancy. These observations therefore represent the converse of those previously reported,[3c,d] and furnish further evidence that the arterial hypertension encountered in true "toxemia of pregnancy" results from undue water retention conditioned by hypoproteinemia. It must, of course, be recognized that other factors than changes in the sodium intake, such as the intake of other electrolytes, the amount of carbohydrate and nitrogen ingested, as well as the water intake itself, may all influence water balance, particularly in the presence of low plasma proteins.

Arterial hypertension observed in the last trimester of pregnancy will be found in the majority of cases, if the data are available, to have been present before pregnancy, and will also be found to persist after the puerperium. In a small number of cases arterial hypertension appears for the first time during pregnancy as a result of the development in pregnancy of acute glomerulonephritis, pyelonephritis, or benign or malignant nephrosclerosis. It is apparent that these conditions should be designated by their proper names. Difficulty in differential diagnosis does not justify the inclusion of these conditions under the term "toxemia of pregnancy." If this misnomer is to be retained—and only long usage can warrant its retention—it should be applied only to the syndrome characterized by the *initial* appearance of arterial hypertension in the last trimester of pregnancy, and its disappearance after the puerperium in women who do not have glomerulonephritis, pyelonephritis, or nephrosclerosis. This syndrome, often referred to as preëclampsia, is of relatively common occurrence.

Methods. Twenty women in the last trimester of pregnancy with arterial hypertension were selected for study. These women comprised two groups, one composed of 10 women known to have had arterial hypertension prior to pregnancy and exhibiting a similar condition after the puerperium, and a second of 10 women who had normal blood pressures prior to, early in, and after pregnancy.

Upon admission to the hospital all the patients were placed upon house diets without restrictions of any sort. They were not put to bed. Salt and water were allowed freely, but no sodium bicarbonate or saline cathartics were permitted. The arterial blood pressures were determined each morning after the patient had been at rest in a chair for at least 20 minutes. On the morning of the third day or later, the patients were placed on a diet consisting of only 1500 cc. of skim milk daily. Water was allowed freely. The rationale of this procedure and its effect upon weight and water retention have been discussed previously.[3f]

Observations. 1. The 10 women with known preëxisting arterial hypertension included 7 with essential hypertension, 1 with polycystic kidneys, 1 with probable chronic pyelonephritis, and 1 with probable chronic glomerulonephritis. Their calculated plasma protein osmotic pressure[4] varied from 217 to 267 mm. of water. They lost from 1.4 to 6.3% of body weight during the 5-day régime of skim milk. In no instance was there a significant change in blood pressure during this period, although hospitalization alone in the preliminary control period was frequently associated with marked declines in blood pressure, particularly in the systolic. Figures 1 and 2 are characteristic records. All the data are summarized in Table 1. In each instance, examination 6 weeks or more postpartum revealed persistent arterial hypertension.

TABLE 1.—THE EFFECT UPON WEIGHT AND BLOOD PRESSURE OF A DIET OF ONLY SKIM MILK IN 10 PREGNANT WOMEN WITH ARTERIAL HYPERTENSION PRIOR TO AND DURING PREGNANCY.

Case, No.	Weight loss, %	Blood pressure change.*		Average "initial" blood pressure.*		Average "final" blood pressure.*		Calculated plasma protein osmotic pressure, mm. H_2O.
		Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	
41	1.4	−13	−8	155	105	142	97	267
42	1.6	−2	+5	145	92	143	97	262
43†	2.5	+2	−5	146	106	148	101	247
44‡	2.5	−22	−9	173	112	151	103	225
45§	3.3	−6	+2	157	94	151	96	237
46	3.6	−5	−1	146	94	141	93	218
47	3.7	−5	−1	140	97	135	96	255
48	3.8	−7	+6	147	80	140	86	232
49	5.5	−2	0	140	96	138	96	217
50	6.3	−9	+3	188	100	179	103	220
Average	3.4	−7	−1	154	98	147	97	238

* The "initial" average blood pressure is the arithmetic average of the blood pressures taken on the 3 days preceding the milk régime, the "final" average is the arithmetic average of the 3 days after the régime, and the change is the difference between these two averages.

† Polycystic kidneys.

‡ Chronic nephritis, probably glomerular.

§ Chronic nephritis, probably pyelonephritis.

It thus appears that the limitation of sodium intake by means of a milk diet resulted in moderate weight losses, but was without significant effect on the arterial blood pressure in 10 women with arterial hypertension in the last trimester of pregnancy who were known to have had hypertension before the pregnancy.

2. The plasma protein osmotic pressures of the 10 women with "toxemia" of pregnancy, as defined above, varied from 172 to 233 mm. of water. These women lost from 3.8 to 8.2% of body weight and became free of visible edema during the period when they received no other food than skim milk. Their arterial blood pressure fell significantly (Table 2). Figures 3 to 7 are characteristic.

Albuminuria decreased in the 9 women who had measurable amounts of albumin in the urine. Five of these 10 women had, besides edema, such preëclamptic symptoms as headache, vertigo, drowsiness, visual disturbances or epigastric pain. Coincident with the loss of weight these symptoms disappeared.

TABLE 2.—THE EFFECT UPON WEIGHT AND BLOOD PRESSURE OF A DIET OF ONLY SKIM MILK IN 10 WOMEN WITH TRUE "TOXEMIA" OF PREGNANCY.

Case. No.	Weight loss, %.	Blood pressure change.*		Average "initial" blood pressure.*		Average "final" blood pressure.*		Calculated plasma protein osmotic pressure, mm. H_2O
		Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	
51	3.8	−34	−26	157	110	123	84	218
52	4.0	−45	−27	163	100	118	73	233
53	4.5	−31	−21	161	98	130	77	222
54	4.8	−32	−17	150	100	118	83	225
55	5.3	−24	−14	151	97	127	83	200
56	5.5	−41	−22	153	112	112	90	222
57	6.0	−27	−12	140	92	113	80	185
58	6.6	−59	−37	189	120	130	83	188
59	7.0	−32	−33	160	116	128	83	172
60	8.2	−40	−38	170	128	130	90	175
Average	5.6	−36	−24	159	107	123	83	204

* The "initial" average blood pressure is the arithmetic average of the blood pressures taken on the 3 days preceding the milk régime, the "final" average is the arithmetic average of the 3 days after the régime and the change is the difference between these two averages.

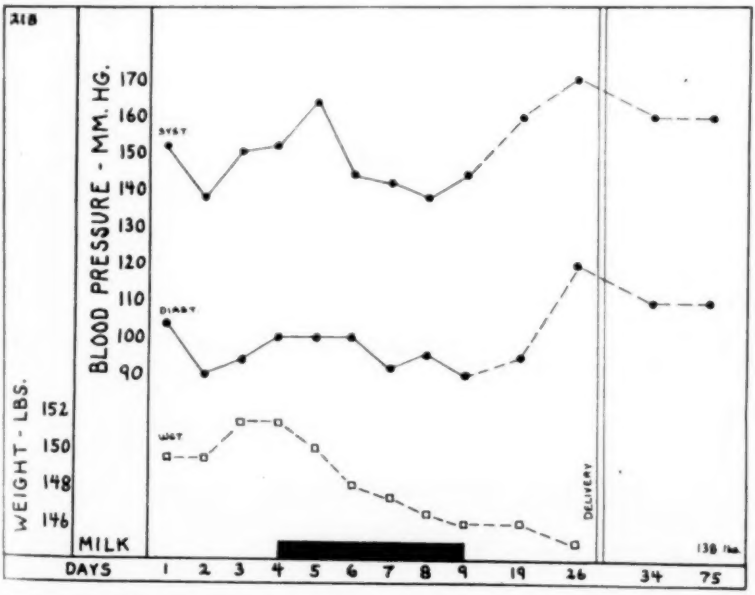

FIG. 1.—Lack of effect of milk diet on blood pressure in case (46) of essential hypertension. Note the rise in pressure in the last week of gestation in spite of continued freedom from water retention and that the blood pressure postpartum was as high as during pregnancy.

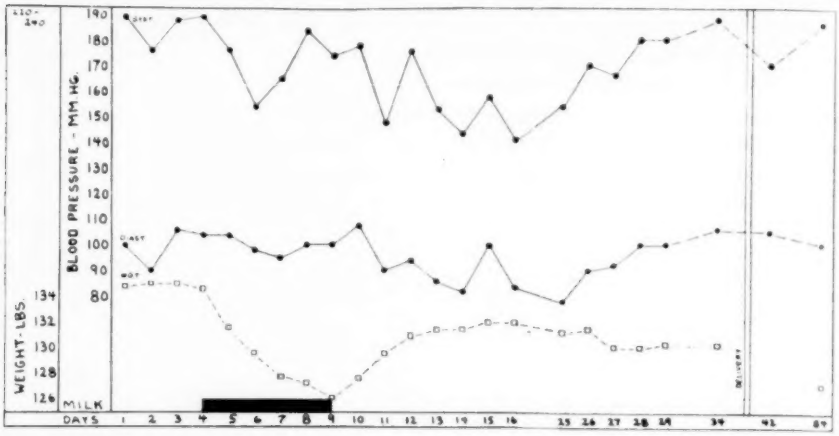

FIG. 2.—Lack of effect of milk diet on blood pressure in case (50) of essential hypertension. Note the slow decline in blood pressure during the first 25 days unrelated to changes in weight; the spontaneous rise in the last 10 days of gestation without gain in weight, and that postpartum the blood pressure was as high as during pregnancy.

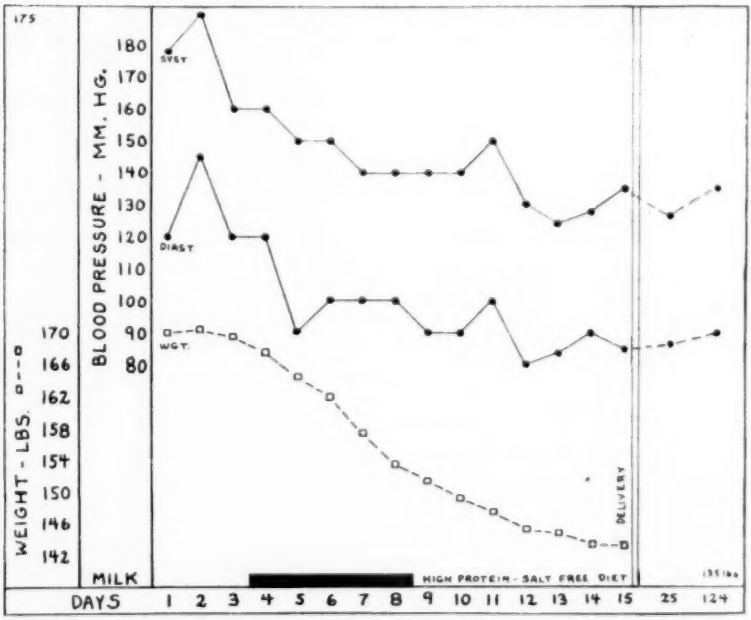

FIG. 3.—Marked fall in blood pressure during milk diet in severe case (60) of true "toxemia" of pregnancy. Note continued normal blood pressure and further weight loss while the patient received a diet containing 150 gm. protein and essentially no salt, and that the blood pressure remain normal postpartum. (In order to show the total loss of 27 pounds in 12 days the weight scale in this figure is smaller than in the other figures.)

Following the period on skim milk these women received a diet which was essentially as free of sodium as practical, which consisted of 150 gm. protein, 100 gm. carbohydrate, and 100 gm. fat. In no instance was there any significant gain in weight on this diet. The arterial blood pressures remained down. Symptoms did not reappear. Albuminuria remained unchanged or decreased further. Parturition and the puerperium were uneventful. Final examinations made postpartum showed normal blood pressures and urines free of albumin.

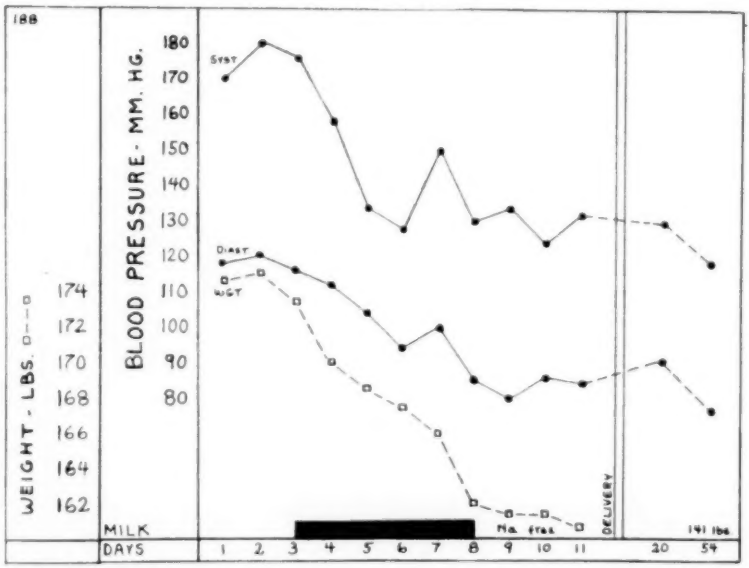

FIG. 4.—Marked fall in blood pressure during milk diet in severe case (58) of true "toxemia" of pregnancy. Note that neither weight nor blood pressure rose while the patient received a diet containing essentially no salt following the milk régime and that the blood pressure remain normal postpartum.

It thus appears that in 10 women with true "toxemia of pregnancy" the plasma protein levels were such that the limitation of sodium intake by means of a milk diet resulted in a marked loss of retained water, preëclamptic symptoms disappeared, the arterial blood pressure fell, and albuminuria diminished.

Discussion. The observations reported here, together with those previously noted,[3] indicate that arterial hypertension and symptoms of preëclampsia in true "toxemia of pregnancy" result from undue water retention conditioned by hypoproteinemia. When the plasma proteins are sufficiently low, so that water retention of significant magnitude may be induced by sodium salts, the arterial blood pressure rises and preëclamptic manifestations may appear,[3c,d] and con-

versely when water retention can be eliminated by acidifying diuretics[3d] or by a low sodium diet, the arterial blood pressure falls and preëclamptic manifestations disappear. These two sets of observations serve as controls for each other. It is hardly conceivable that hospitalization or spontaneous fluctuation could have been responsible for the rise in blood pressure previously reported in 10 pregnant women given sodium,[3d] the fall in blood pressure in the 10 pregnant women deprived of sodium here recorded and the fall in blood pressure hitherto noted[3d] in the 3 given ammonium chloride.

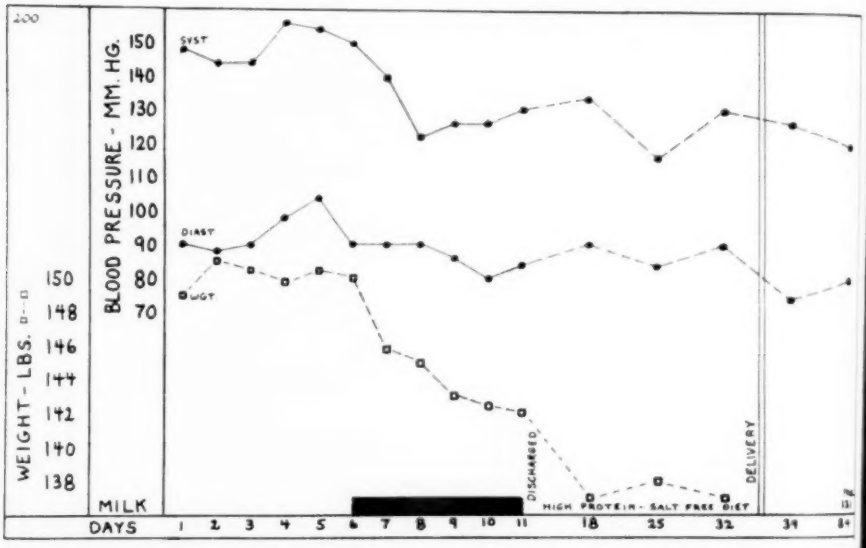

FIG. 5.—Marked fall in blood pressure during milk diet in moderately severe case (55) of true "toxemia" of pregnancy. Note the stationary weight and blood pressure during the control period before the milk régime was commenced, and that the weight remained down and the blood pressure normal during the last 3 weeks of gestation while the patient received *at home* a diet containing 150 gm. protein and essentially no salt; postpartum the blood pressure remained normal.

Furthermore, just as it has been shown previously that sodium salts do not produce increases in hypertension in pregnant women when the plasma protein levels are such that marked water retention does not occur,[3c,d] it has now been demonstrated that in similar patients a low sodium intake does not result in a fall in arterial blood pressure.

It therefore appears that the response to sodium administration or withdrawal may serve as a means of differentiating between the hypertension observed in true "toxemia of pregnancy" and that of vascular or renal disease in which the pregnancy is but an episode. However, if the plasma protein concentration is exceedingly low, the withdrawal of sodium may have little if any effect on water

retention. This is true in non-pregnant individuals as well as in pregnant women. *Under these circumstances sodium withdrawal has no significant effect upon the arterial blood pressure even though the patient has true "toxemia."*

There is reason to believe that arterial hypertension in general, whether this be due to vascular disease, renal disease, coarctation of the aorta, or "toxemia of pregnancy" is due to arteriolar constriction, either in the form of actual organic change in the arteriolar wall or of spasm. The temporary nature of the hypertension in "toxemia" suggests that spasm is responsible. However, discussion of the mechanism of arteriolar constriction in "toxemia" of pregnancy is beyond the scope of this paper. The fact remains that

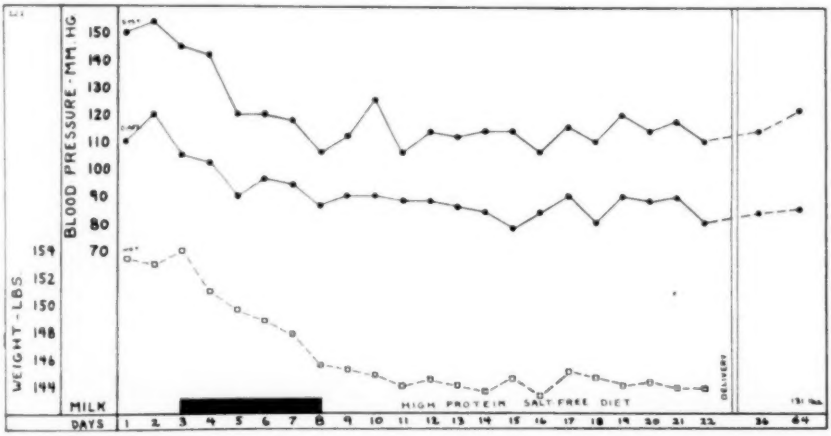

FIG. 6.—Fall in blood pressure during milk diet in moderately severe case (56) of true "toxemia" of pregnancy. Note that the weight remained down and the blood pressure normal during the last 3 weeks of gestation while the patient received a diet containing 150 gm. protein and essentially no salt; postpartum the blood pressure remained normal.

arterial hypertension in this condition is responsive to changes in water balance. Why some patients may have rather marked water retention without arterial hypertension can not be stated at this time. In a number of instances marked water retention has been observed for a period of several weeks before arterial hypertension appeared and in others parturition has supervened without hypertension ever manifesting itself. Whether these women would have eventually developed hypertension had pregnancy continued longer cannot be said. Although there is no evidence for such a belief it is possible that some individual or constitutional susceptibility to hypertension is necessary in order that water retention may produce hypertension during pregnancy.

All of the patients diagnosed as true "toxemia" in this series continued to have normal blood pressures when reëxamined from 6 weeks to 4 months after parturition, although albuminuria persisted postpartum in some patients for as long as 2 months before disappearing. Although a number of women who have had eclampsia have been examined as late as 15 years afterward without showing any evidence of vascular or renal disease, many others show definite evidence of such abnormalities. In most instances in which data were available it was found that these women had had vascular or

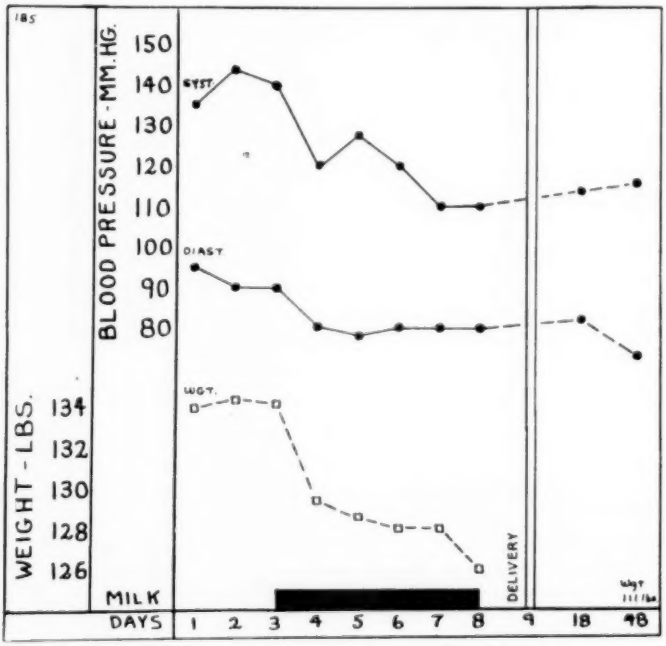

FIG. 7.—Fall in blood pressure during milk diet in mild case (57) of true "toxemia" of pregnancy. Note blood pressure continued normal postpartum.

renal abnormalities prior to pregnancy, and hence were not suffering from true "toxemia" of pregnancy at the time they had convulsions. However, it is easily conceivable that prolonged "toxemia" may result in permanent renal or vascular damage although in none of approximately 80 patients with true "toxemia" has this been observed. There is also little doubt that the syndrome of "toxemia" may be superimposed upon chronic vascular or renal disease or may complicate acute pyelonephritis in pregnancy. In the former instance one would obviously have evidence of vascular or renal damage prior to pregnancy with an exacerbation of manifestations

during gestation and a return postpartum at best only to the pre-pregnant state.

The absence of an effect of a low sodium intake on essential arterial hypertension in pregnancy may be compared to similar observations in non-pregnant subjects with this condition,[1,2]

It is to be remembered that although a low sodium régime may free the patient of retained water, result in a fall of arterial blood pressure to normal and cause headache, drowsiness, vertigo, and visual disturbances to disappear, such a régime does not alter the fundamental disturbance: hypoproteinemia. These patients remain in unstable equilibrium as long as the plasma colloid osmotic pressure remains at a level at which it is constantly in danger of being overbalanced by the intracapillary hydrostatic pressure. "Cure" cannot be effected unless the plasma proteins can be caused to return to normal. Since "toxemia" occurs late in pregnancy, when fetal demands for protein are large, and since hypoproteinemia probably signifies not only a low plasma protein level but also a depletion of the organism's reserve stores of protein, one must not expect a rapid increase in plasma protein values during the remainder of gestation even with intensive protein feeding. It is possible that the intravenous infusion of concentrated plasma protein ("lyophile" serum) may be of value. However, any procedure which alters the blood volume of such patients may upset their unstable equilibrium and precipitate serious results.

A question which inevitably must arise is whether non-pregnant individuals with similar hypoproteinemic edema show the same phenomena regarding blood pressure as do these women. It is true, of course, that the usual type of non-pregnant patient with hypoproteinemia seen in American hospitals suffers from cirrhosis, nephrosis, anemia, tuberculosis, colitis or other debilitating disease which may alter the reactivity of his vascular system. However, it appears probable that certain peculiarities of the pregnant state itself may be responsible for this unusual behavior of the vascular system to water retention. Some of the *known* physiologic alterations which are present in pregnancy are an increased blood volume, an increased cardiac output, a moderate elevation of venous pressure, and probably moderate mechanical pressure by the enlarged uterus on the ureters and on the renal veins. Although various tests fail to reveal any consistent changes in renal function in "toxemia" of pregnancy the fact that albuminuria is generally present in itself indicates that there is a disturbance of the kidney even though histologic examination fails to reveal anything more than cloudy swelling. The real nature of this disturbance and its possible relationship to the occurrence of hypertension as a result of water retention are unknown. The rôle of hormonal changes in pregnancy is so little understood that discussion is unwarranted. However, the observa-

tion that, in true "toxemia" parturition may be followed by diuresis, loss of edema, decrease in blood volume, and increase in plasma protein concentration before there has been time for much actual regeneration of plasma protein, speaks for the belief that some phenomena normally occurring in pregnancy are involved in the response to water retention.

Since hypoproteinemia is the factor which permits the development of the condition of true "toxemia," adequate prenatal care must include attention to this. Although disturbances of absorption, assimilation, manufacture and urinary loss of protein may be involved, it appears that the chief cause of hypoproteinemia in pregnancy lies in an inadequate dietary intake of protein, especially in view of the increased demands for protein for the developing fetus and also for the maternal organism. It is therefore of paramount importance that the diet in pregnancy contain more, not less, protein than an adequate diet for non-pregnant subjects.

Conclusions. 1. Arterial hypertension in pregnancy due to pre-existing primary vascular or renal disease is not influenced by alterations in water balance.

2. True "toxemia" of pregnancy is the result of undue water retention conditioned by hypoproteinemia.

3. Arterial hypertension and preëclamptic manifestations such as edema, headache, vertigo, drowsiness, and visual disturbances, in the true "toxemia" of pregnancy may be relieved by measures which eliminate undue water retention.

4. Study of the behavior of pregnant women with hypertension after changes in water balance may serve to differentiate true "toxemia" from primary vascular and renal disorders.

5. A diet low in sodium has been shown to be one successful way to decrease or eliminate signs and symptoms of true "toxemia" of pregnancy.

6. The development of true "toxemia" of pregnancy can probably be prevented by maintaining the pregnant woman's plasma proteins at a normal level by adequate diet.

Since this manuscript was submitted for publication corroborative results have been obtained in 25 additional cases.

The writer is indebted to Dr. F. H. L. Taylor and Miss Margaret Adams for carrying out the chemical determinations reported in this paper.

This work was made possible through the coöperation of the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, to whom the writer acknowledges his indebtedness.

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OBSERVATIONS ON REFERRED PAIN OF CARDIAC ORIGIN.*

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The most commonly employed objective test for the diagnosis of angina of effort is the exercise tolerance test. Several investigators have been successful in inducing an anginal attack[4,6] by the use of exercise on a standard stairs or by hopping on one foot. This method has failed to give as many positive tests in our hands (Katz and Korey[2]) as reported by others.[4,6] The use of epinephrin[5] or anoxemia[7] to induce an anginal attack we have found to be too unreliable and hazardous.[3] We have developed a new method, simple in its application and less hazardous to the patient, which gave positive findings in many more patients than did the exercise tolerance test. This test consists of inflating an ordinary blood pressure cuff placed on the left arm above the elbow to 50 mm. of mercury above the systolic blood pressure reading. The inflation is continued for five minutes or until cardiac pain is elicited from the patient who does not anticipate such pain. The latter was considered a positive cuff test; its absence constituted a negative cuff test.

The cuff test was tried first on 25 control patients, 40 to 55 years of age, in whom no evidence of heart disease was present. The test was negative in all, the patients complaining only of tingling and pain in the arm distal to the inflated cuff.

The cuff test was then tried on 93 patients of whom 24 had a definite clinical story of angina pectoris, 39 had a questionable clinical story and the remaining 30 had heart involvement but no clinical history of angina. The last two groups included many so-called neurotic patients. The results of the cuff test are shown in Table 1:

Table 1.—Analysis of Data.

Type of case.	No. of patients tested.	No. of positive cuff tests.	No. of positive exercise tolerance tests.
"Non-cardiac" controls	25	0	*
Heart disease and no angina pectoris	30	0	0
Questionable angina pectoris	39	0	0
Definite angina pectoris	24	19 (80%)	4 (17%)

* No exercise tolerance tests done.

Nineteen positive cuff tests were obtained, all being present in patients in whom a definite clinical history of angina was known. Such a positive cuff test consisted in the development of precordial

* Aided by the A. D. Nast Fund for Cardiac Research.

pain or oppression which the patient stated was similar to the onset of his spontaneous attacks. Only 4 of these patients had a positive exercise tolerance test. In 11 patients in whom pain was produced by the cuff test, nitroglycerin, $\frac{1}{150}$ grain, was given because of the severity of the precordial pain. In 6 of these patients, the cuff was again applied 15 minutes after the attack of pain had been relieved by nitroglycerin, without again eliciting precordial pain. Using the cuff test on the right arm or the right or left legs gave negative results, except in 3 patients who had a definite clinical story of radiation of the pain down the right arm only; in these 3 patients the cuff test was negative on the left arm and legs but positive on the right arm.

The cuff test was repeated on subsequent visits on several patients. While in some it remained negative or positive as on the first visit, in others the test previously positive became negative or *vice versa*. Our data are too scanty to determine the exact cause of this variability, but it would appear to be related to the same emotional and physical factors that lead to the variability in the frequency of spontaneous anginal attacks.

Our experience with this cuff test suggests that while a negative test does not rule out angina pectoris, a positive test is indicative of its presence. It may be found, if further experience confirms these results, that the cuff test may have a place as an aid in the diagnosis of angina pectoris where objective evidence is required to supplement an unreliable history.

As regards the mechanism of a positive cuff test, we may consider three possibilities: 1, A reflex vasoconstriction of the coronary arteries initiated over the segmental distribution of the referred pain; 2, a psychogenic trigger reaction whereby one part of the painful state of angina, the pain in the ischemic arm, sets up in susceptible individuals the entire syndrome; this is in reality a form of so-called conditioned reflex; or, 3, a spatial summation of stimuli coming up from the heart and from the forearm which by using a final common path to the central site of pain perception, convert what otherwise would be subthreshold stimulation for an anginal attack into threshold stimulation. Adrian and his associates[4] have demonstrated the importance of such spatial summation of sensory impulses. Further work is required to differentiate between these possible mechanisms. However, our study has shown, we believe, that one of the variables responsible for an anginal attack is not only the condition of the heart itself, but also that of the sensory regions to which the anginal attack is referred. That this is so has been demonstrated also by the work of Soma Weiss[8] on the soothing effect of local anesthesia of the region to which pain is referred.

In order to test for the possibility of reflex coronary vasoconstriction, electrocardiograms were taken in a series of 12 patients before and during the carrying out of the cuff test. In 5 patients in

whom the test produced either definite precordial pain, an increase in the existing precordial pain or a sense of pressure over the sternum, the electrocardiogram showed no change during the test, nor was there any change in the 7 patients who developed no precordial pain. It is noteworthy that in one of the patients with a previous coronary occlusion and definite electrocardiographic deformities, complaining of persistent precordial pain before the test was begun, the aggravation of the precordial pain following the cuff test was not accompanied by any change in the electrocardiogram taken during the height of the precordial pain. These results would seem to rule out the possibility that precordial pain following the cuff test was due to a reflex coronary vasoconstriction.

Summary. A method was developed for inducing an anginal attack in susceptible patients with their permission. This was successful in 19 out of 24 patients with definite clinical angina pectoris. It was not successful in producing an anginal attack in any of the 55 cardiac and "non-cardiac" controls nor in any of the 39 patients with doubtful clinical angina pectoris.

The method consisted of producing 5-minute ischemia in the left arm by raising the pressure in a blood-pressure cuff on the arm to 50 mm. Hg above systolic pressure. This cuff test was positive on the right arm and not on the left arm in 3 patients in whom the pain was referred to this arm.

The possible mechanisms involved are discussed. The ability to induce angina in this way serves to emphasize the neuropsychic aspects of the anginal attack and offers another cause for the variability in its occurrence.

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PARADOXICAL EMBOLISM.*

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In 1860, Cohn[3] observed that emboli in the right side of the heart can enter the systemic circulation through defects in the cardiac

* Extract from thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

septum. In 1876, Cohnheim[4] traced the path of an embolus through an opening in the interatrial septum. An embolus was found in the right cerebral artery and thrombosis of the veins of the lower extremities had occurred. In 1881, Zahn[17] demonstrated a long embolus that had partly passed through a patent foramen ovale. Extensive thrombosis of the iliac veins also was found. Hauser[7] reported a similar case in 1888. Rostan,[14] in an analysis of 711 postmortem examinations, found the foramen ovale occluded by an embolus in 3 instances and he expressed the opinion that in 7 cases the embolus found in the systemic circulation had passed through a patent foramen ovale. He called this condition "crossed embolism." It was von Recklinghausen who suggested the term "paradoxical embolism." There have been reports by Ohm,[12] Versé[16] and Beattie[2] similar to those mentioned.

Abbott,[1] after analyzing 1000 cases of congenital heart disease in which necropsy had been performed, reported 12 cases of paradoxical embolism associated with patency of the foramen ovale, interventricular septum, and ductus arteriosus. In 1935, Hirschboeck[8] reported a case with a review of the literature. In 1936, Neely,[11] and also Jones,[9] added a similar case.

Koritschoner[10] recorded a case with bibliography but he did not include the cases of Neely and Hirschboeck. He did, however, refer to 2 cases not included in other bibliographies. His statement that 12 cases had been recorded would seem inaccurate but, adding the 2 cases which he omitted, and that of Jones, brings the total to 15.

When pulmonary embolism occurs, it usually follows thrombosis of the systemic veins. Less frequently it is associated with thrombi in the right side of the heart and rarely it is attributable to primary tumors of the heart or to tumor fragments which have invaded the systemic veins.

Emboli of the systemic circulation have many possible sources. They may be dislodged from thrombi in the left side of the heart, associated with disease of the aortic or mitral valves, or from mural thrombi overlying a myocardial infarct or primary tumor. Emboli may arise also from fragments of athermatous ulcers or from a region of aneurysmal dilatation of the aorta or large arteries. The pulmonary veins occasionally transport emboli from a diseased lung to the left side of the heart. This is particularly true of pneumonia, abscess and gangrene, tuberculosis and tumors. Emboli may arise in the systemic veins or right side of the heart and cross through a patent foramen ovale to the systemic arterial circulation.

As Gross[5] and others have shown, the pressure in the left atrium is sufficient to make the valvelike flap over the foramen ovale competent, but conditions which reverse the existing pressures cause incompetence and make it possible for emboli or blood to flow from the right atrium directly into the left atrium.

Haggart and Walker,[6] by observing the effect of graded occlusion

of the pulmonary arteries on the pulmonic and systemic circulation, have demonstrated that sudden occlusion of the left branch of the pulmonary artery causes an immediate rise in pulmonary pressure, averaging about 29%, and following total pulmonary occlusion, the pulmonary pressure increases rapidly, 121 to 267%. At the same time there was an immediate fall in the systemic arterial blood pressure. This coincidence allows the flow of a current of blood from the right atrium to the left atrium, provided the foramen ovale is patent. Thompson and Evans[15] concluded that more than a third of the pulmonary circulation must be occluded before paradoxical embolism can occur. They also stated that if the circulation is depleted more than 50%, death usually occurs within 10 to 30 minutes. In about 50% of the cases "crossed emboli" are preceded by the occurrence of pulmonary embolism; but it is not to be assumed that the presence of a patent foramen ovale with pulmonary embolism always will result in paradoxical embolism.

Six cases of paradoxical embolism are reported in this series. In each case paradoxical embolism was preceded by pulmonary embolism; 3 patients died suddenly and 3 survived long enough for infarcts to develop in other organs. Major surgical operations were performed in 5 cases and 1 was strictly a medical case. In each case, postmortem examination revealed an embolus in transit through the foramen ovale. The average age was 54 years; 3 patients were women and 3 were men.

In addition, a case is reported in which a cerebral abscess developed, probably at the site of a previous paradoxical embolism.

Case Reports. Case 1.—An obese white man, aged 45, was operated on for subacute cholecystitis with cholelithiasis. Seven days postoperatively, pain developed in the muscles of the calf of the right leg and there was some tenderness over the right anterior saphenous vein. Four days later there occurred a sudden onset of marked pulmonary edema, productive cough, profuse perspiration, and labored respirations with moderate cyanosis. Seven days later pain developed in the right side of the thorax; the pain was exaggerated by breathing. This episode was followed by grayish pallor and profuse sweating. The patient's condition gradually became worse and he died 21 days after operation. *Necropsy* revealed pulmonary embolism and an embolus extending through an anatomically patent foramen ovale; also there were infarcts of the left kidney (paradoxical embolism). The embolus that passed through the patent foramen ovale was 10 cm. long and 5 mm. in diameter (Fig. 1).

Case 2.—An obese white woman, aged 62, was operated on for subacute, perforating cholecystitis with stones. Her course was uneventful until the 12th postoperative day when pneumonia developed in the lower lobe of the right lung. On the 16th day, she experienced severe substernal pain with evidence of shock and delirium. On the 20th day, right hemiplegia was evident. Death occurred on the 23d postoperative day. *Necropsy* revealed thrombosis of the left posterior cerebral artery, thrombosis of the right auricular appendage, infarction of the right lung, thrombosis of the left pulmonary artery (embolism questionable). The foramen ovale was patent and a clot was found extending through the opening.

CASE 3.—An obese white man, aged 56, was operated on for a suspected ulcerating prepyloric lesion. Two days after operation respiratory infection developed but the patient recovered; 8 days later pain developed in the right anterior part of the thorax. The pain became more severe and was followed by cyanosis. The man rallied slightly but then suddenly became worse and death occurred 12 days after operation. *Necropsy* revealed pulmonary embolism and infarction of the right lung. There was a patent foramen ovale with an embolus extending through it from the right auricle into the left auricle. There were also multiple infarcts of the kidneys.

FIG. 1.—Patent foramen ovale with an antemortem embolus extending through it. View of the left auricle.

CASE 4.—A white woman, aged 56, was operated on for a peptic ulcer. Her course was uneventful until 7 days after operation when she had several attacks of stabbing pain in the right side of the thorax followed by the production of bright red sputum. Two days later she suddenly experienced thoracic pain and this was followed by cyanosis and death. *Necropsy* revealed bilateral pulmonary embolism arising from thrombosis of the iliac veins and inferior vena cava. There was an embolus in the right auricle which projected through a patent foramen ovale. It extended a distance of 1.5 cm. into the left auricle.

CASE 5.—A white man, aged 48, was operated on for carcinoma of the rectum. Convalescence was satisfactory until 17 days after operation when pain, swelling, and tenderness developed over the left femoral vessels. On the 20th postoperative day he had several attacks of dyspnea with pain in the thorax; these symptoms were followed by sudden death. *Necropsy* disclosed, in addition to pulmonary embolism, an embolus 8 cm. in length in the right auricle, projecting through a patent foramen ovale into the left auricle.

Case 6.—An obese white woman, aged 54, who gave a history of excessive thirst and urination for 6 weeks previously, had been treated for diabetes mellitus. Acidosis was controlled by administration of insulin and fluid and by diet. Two days after her admission, while she was sitting up in bed, she suddenly became dyspneic and cyanotic, and died. *Necropsy* revealed a pulmonary embolus and also an embolus in the right auricle which projected for a distance of 3 cm. into the left auricle, through a patent foramen ovale.

Diagnosis and Prognosis. The diagnosis of paradoxical embolism while the patient is living is made with reservation and is subject to criticism. However, in the presence of venous thrombosis followed by pulmonary embolism and recovery, together with evidence of infarction in other organs, one is justified in suspecting that crossed embolism has occurred. If the acute attack is succeeded by cerebral symptoms, one may consider the diagnosis more positively.

Prognosis depends on the course during the period immediately following the acute episode. The prognosis is almost always unfavorable.

Sequelæ. As a sequel of paradoxical embolus, brain abscess has been reported. Rabinowitz, Weinstein and Marcus[13] reported a case which they regarded as one of paradoxical brain abscess complicating the tetralogy of Fallot. In a review of the literature, they could find 10 cases besides their own; 6 of the 10 cases had been presented by Abbott and Beattie. They concluded that paradoxical abscess is more common in association with interventricular septal defects than in association with interatrial defects, particularly when there is dextroposition of the aorta. The sudden onset of cerebral symptoms in a case of congenital heart disease, particularly when there is a septal defect, should make one suspicious of paradoxical brain abscess.

Following is a report of a case in which a paradoxical cerebral abscess was suspected:

Case 7.—A white woman, aged 39, had been examined at the clinic for the first time when she was 19. At that time a diagnosis of congenital heart disease had been made on the basis of cyanosis and clubbing of fingers since childhood, with marked palpitation and dyspnea on exertion. Physical examination had revealed moderate cyanosis of the lips and fingers, with clubbing. The heart was reported to have been slightly enlarged and a systolic murmur had been found at the apex. In the 20 years since her first admission, she had been often seen because of dyspnea and palpitation. At the examination made when she was 39, there was little change in her cardiac condition. Roentgenograms gave evidence of moderate cardiac enlargement, particularly in the region of the conus. The electrocardiogram demonstrated right ventricular preponderance. Studies of the blood indicated a mild compensatory polycythemia. The complaint made on her admission at the age of 39 was that, 1 week before, a respiratory infection had developed. Three days after its onset, she had noticed numbness of her right hand and of the right side of her face, accompanied by twitching and transient swelling of the right arm, and a sense of constriction around her heart. Three similar attacks had taken place within the next 2 weeks. Because of localizing neurologic symptoms and signs, temporoparietal

exploration and decompression were performed. Death occurred on the 13th postoperative day.

Necropsy revealed an abscess in the left cerebrum. The heart weighed 310 gm. There was a patent foramen ovale, 2.5 cm. in diameter, an old thrombus in the pulmonary artery with marked arteriosclerosis and moderate dilatation of the pulmonary artery, and moderate hypertrophy of the right ventricle.

TABLE 1.—SUMMARY OF REPORTED CASES.

Case.	Age, yrs.	Sex.	Clinical diagnosis.	Anatomic diagnosis.
1	45	Male	Subacute cholecystitis with cholelithiasis	Pulmonary embolism through patent foramen ovale
2	62	Female	Subacute perforating cholecystitis and cholelithiasis	Thrombosis posterior cerebral and left pulmonary artery; embolus through patent foramen ovale
3	56	Male	Ulcerating prepyloric lesion	Pulmonary embolism; infarction right lung and both kidneys; embolus through patent foramen ovale
4	56	Male	Peptic ulcer	Bilateral pulmonary embolism; thrombosis iliac veins and inferior vena cava; embolus through patent foramen ovale
5	48	Male	Carcinoma of rectum	Pulmonary embolism; embolus through patent foramen ovale
6	54	Female	Diabetes mellitus	Pulmonary embolism; embolus through patent foramen ovale
7	39	Female	Congenital heart disease; brain abscess	Abscess left cerebrum; patent foramen ovale

Comment. The cases reported (tabulation) illustrate one of the results of what is referred to, generally, as a benign cardiac malformation, that is, the patent interauricular septum. Although paradoxical embolism is interesting from the pathologic point of view and is usually termed a pathologic curiosity, it is not without clinical interest. The diagnosis of a paradoxical or crossed embolism rarely is made during the life of the patient because there are few indicative signs or symptoms. Furthermore, death from pulmonary embolism usually occurs so rapidly that there is little time for evaluation of the presenting clinical syndrome. However, the diagnosis may be suggested by the presence of pulmonary and congenital heart disease. Careful appraisal of all the signs and symptoms, with the thought of paradoxical embolism in mind, may aid in a more frequent antemortem diagnosis. Even without the clinical diagnosis of congenital heart disease, the syndrome of pulmonary embolism followed by multiple infarction in the organs supplied by the systemic circulation should suggest that paradoxical embolism may have occurred. In all of the 7 cases reported there were defects of the interauricular septum, but in only 1 were there signs or symptoms of congenital heart disease. Paradoxical brain abscess is the rarest complication of paradoxical embolism.

Conclusion. The diagnosis of paradoxical or crossed embolism is rarely made while the patient is alive. There are few signs or symp-

toms indicative of such a process. However, the diagnosis may be suggested by the presence of pulmonary embolism and congenital heart disease. In all of the 7 cases reported, there were interatrial septal defects, but in only one were there signs or symptoms of congenital heart disease.

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RADIOLOGIC MEASUREMENTS OF THE APICO-BASAL RELAXATION OF THE LUNG DURING ARTIFICIAL PNEUMOPERITONEUM TREATMENT.

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During recent years publications have appeared in the medical literature in which the problem of treating pulmonary tuberculosis by artificial pneumoperitoneum was discussed.[1a, 7] Subsequent clinical observations seem to confirm the assumption that repeated injections of oxygen or air into the peritoneal cavity exert a favorable effect upon certain types of tuberculous lesions of the lung.[1b,c, 2–6] The favorable influence is attributed to the elevated position of the diaphragm, which, in turn, causes a pulmonary relaxation. It is reasonable to assume that a sufficient degree of pulmonary relaxation induced by pneumoperitoneum might lead to mechanical, circulatory, and immunologic changes in the lung similar to that which follow surgical paralysis of the phrenic nerve, or artificial pneumothorax.

With the patient in the upright position the injected gas occupies the area underneath the diaphragm. The fluoroscopic or roentgenographic appearance of the gas suggests a rather marked upward displacement of this muscle. I[1b] have pointed out in a previous publication that the area occupied by the gas does not signify a corresponding upward displacement of the diaphragm, but it is

partly made up by a descent of the subdiaphragmatic organs. Because of the fact that there is no report in the literature dealing with the accurate measurement of the elevation of the diaphragm in a series of cases treated by pneumoperitoneum, I wish here to present data related to this question.

Method. A group of 40 patients who were receiving pneumoperitoneum treatment for their pulmonary tuberculosis was studied roentgenologically. Of these, 11 were in the moderately advanced stage and 29 in the far-advanced stage (Nat. Tubere. Assn. classification). Roentgenograms taken before and during the treatment were compared. The amount of injected air at each treatment varied from 500 to 1000 cc. Measurements were made in 32 cases after 1 treatment; in 1 case after 2 treatments; in 7 after 3; in 6 after 4; in 2 after 5; in 8 after 6; in 2 after 7; in 2 after 8; in 7 after 10; in 1 after 11; in 3 after 12; in 1 after 14; in 2 after 15; in 4 after 16; in 1 after 20; in 4 after 22; and in 1 after 23 treatments. The treatments were given at weekly intervals at the beginning and 2 weeks apart when the pneumoperitoneum was well established. Roentgenograms were taken at maximum inspiration and at maximum expiration in every instance. Thus, including the films taken before treatment, 248 chest films were measured and analyzed. The exposure was made with the patient in the upright position, from a distance of 6 feet. The apico-basal diameter was measured from the highest point of the apex of the lung to the highest point of the corresponding dome of the diaphragm.

The upward displacement of the diaphragm is influenced by several factors: 1, the tonicity and integrity of the diaphragm (diaphragmatic atony, presence or absence of adhesions); 2, the tonicity of the abdominal wall (inherent anatomic status, reflex relaxation or contraction in response to the injection of air); 3, pathologic changes in or surgical status of the lung (contracting, fibrosing tuberculosis, "spontaneous" paralysis of the diaphragm, massive or partial atelectasis, artificial pneumothorax, surgical paralysis of the phrenic nerve, thoracoplasty, large pleural effusion); 4, the type of breathing (there is a greater tendency toward collection of air underneath the diaphragm in individuals with distinctly thoracic type of breathing than in the thoracic-abdominal or abdominal type of breathing); 5, the amount of air injected.

Following the first pneumoperitoneum treatment there was no change in the position of the diaphragm (2 mm. or less), in 8 of the 32 cases in this group. The maximum elevation of the right and left dome of the diaphragm on inspiration and expiration is given in Table 1.

The figures representing the actual rise of the diaphragm compare favorably with the elevation of the diaphragm after phrenic nerve block. I[d] have studied a comparable group of 30 patients who had a surgical paralysis of the phrenic nerve by the same roentgenologic method and found that the rise after phrenic operation was, on inspiration, 4 cm. or more in 4 (of these there was only 1 as high as 6.3 cm.); 3–3.9 cm. in 10; 2–2.9 cm. in 4; 1–1.9 cm. in 7; less than 1 cm. in 2; and it was absent in 3; in expiration the rise was 4 cm.

or more in 2 (the maximum was 4.5 cm.), 3–3.9 cm. in 1; 2–2.9 cm. in 7; 1–1.9 cm. in 11; less than 1 cm. in 8; and it was absent in 1.

TABLE 1.—MAXIMUM ELEVATION OF THE DIAPHRAGM IN CENTIMETERS AFTER VARYING NUMBER OF PNEUMOPERITONEUM TREATMENTS.

Number of cases		32	1	7	6	2	8	2	2	7	1	3	1	2	4	1	4	1
Number of treatments		1	2	3	4	5	6	7	8	10	11	12	14	15	16	20	22	23
Right	Inspiration	4.2	3.2	2.6	2.3	5.6	3.2	4.4	4.3	5.1	1.8	5.8	3.5	3.5	2.4	5.2	6.0	7.3
	Expiration	4.5	3.1	2.0	2.6	3.6	4.8	2.6	4.7	5.2	1.6	5.3	4.4	6.4	2.7	4.0	4.9	5.8
Left	Inspiration	4.2	2.7	3.2	2.5	3.6	2.5	4.2	3.8	3.8	2.0	6.1	4.0	3.2	3.2	2.5	6.4	5.4
	Expiration	2.8	3.5	3.0	2.4	3.0	4.0	3.1	5.1	3.9	2.0	5.8	4.3	6.4	2.9	5.7	4.8	5.6

TABLE 2. MAXIMUM INDICES OF APICO-BASAL RELAXATION REPRESENTING THE PERCENTAGE BY WHICH THE ORIGINAL APICO-BASAL DIAMETERS WERE REDUCED.

Number of cases		32	1	7	6	2	8	2	2	7	1	3	1	2	4	1	4	1
Number of treatments		1	2	3	4	5	6	7	8	10	11	12	14	15	16	20	22	23
Right	Inspiration	18.6	15.2	11.3	10.0	25.0	19.9	19.5	20.5	30.0	8.5	20.7	14.8	15.7	18.1	25.6	23.6	32.8
	Expiration	18.0	15.5	11.2	12.9	17.5	22.6	11.2	23.5	32.6	8.3	27.2	19.0	31.5	17.5	22.1	22.0	30.2
Left	Inspiration	18.3	12.0	12.5	10.6	13.8	25.2	17.5	17.0	16.9	9.6	25.3	15.6	13.6	16.8	13.1	27.0	22.9
	Expiration	9.4	16.8	12.2	11.1	13.7	22.8	11.0	24.6	20.3	10.1	30.0	16.8	25.7	17.4	34.3	25.0	27.1

A better estimate of the upward displacement of the diaphragm can be gained when one compares the decrease in the apico-basal distance with the length of the apico-basal diameter before treatment. The quotient representing this relation can be designated as the index of apico-basal relaxation. It is calculated according to the following formula: Decrease in the apico-basal diameter divided by the original apico-basal diameter and multiplied by 100. For example, in Case 10 the decrease in the apico-basal diameter was 4.2 cm. on the right side on inspiration after the first treatment; the original apico-basal distance was 22.5 cm.; the index of apico-basal relaxation was $(4.2/22.5) \times 100$ or 18.6. In other words, the apico-basal diameter was reduced by 18.6%.

A comparison was made between the degrees of apico-basal relaxation in inspiration and in expiration. The analysis of the right and left lungs in 84 instances comprises 168 measurements. The index of apico-basal relaxation was equal during the two respiratory phases in 11; it was greater on expiration than on inspiration in 100, and it was smaller on expiration than on inspiration in 57 measurements.

The indices of apico-basal relaxation on the more involved and on the "good" side were compared in 18 instances, including cases that

had 10 treatments or more. It was found that the relaxation of the two sides was approximately equal on inspiration and expiration in 4, on inspiration in 1 and on expiration in 5. The relaxation on the "good" side was greater than on the diseased side in both respiratory phases in 1, on inspiration in 7, on expiration in 1. The relaxation on the diseased side was greater than on the "good" side in both respiratory phases in 3, on inspiration in 2, and on expiration in 4 instances.

As to the changes in the position of the diaphragm during the course of pneumoperitoneum treatment, some illustrative cases can be cited.

Case Abstracts.—Case 1. E. G., aged 30, male, had a far-advanced pulmonary tuberculosis of 7½ years' duration. The first treatment with the injection of 500 cc. of air caused no elevation of the diaphragm, except a 1.6 cm. rise on the left side during expiration. Following the third treatment with the injection of 600 cc. of air the rise was on the right side on inspiration 0.8 cm. (3.9% of the apico-basal diameter), and on expiration 2 cm. (11.2%); on the left side on inspiration 1.5 cm. (7.8%), and on expiration 2.2 cm. (12.2%). After the injection of 700 cc. of air on the 22d treatment, the rise was on the right side on inspiration 2.4 cm. (11.9%), and on expiration 3.5 cm. (19.6%); on the left side on inspiration 3 cm. (15.7%), and on expiration 3.7 cm. (20.5%).

Case 2.—G. E., aged 21, male, had a far-advanced pulmonary tuberculosis of 1½ years' duration. First treatment: amount: 500 cc.; rise of right dome of diaphragm on inspiration 1.7 cm. (7.6%), on expiration 0.8 cm. (4.1%); rise of the left dome of the diaphragm on inspiration 0.9 cm. (3.8%), on expiration 0.5 cm. (2.4%). Sixth treatment: amount: 1000 cc.; rise on the right side on inspiration 3.2 cm. (14.4%), on expiration 1.4 cm. (7.2%); on the left side on inspiration 2.7 cm. (11.4%), on expiration 1.8 cm. (8.7%). Twelfth treatment: amount: 1000 cc.; rise on the right side on inspiration 4 cm. (18%), on expiration 1.9 cm. (10%); on the left side on inspiration 3.4 cm. (14.4%), on expiration 3.5 cm. (16.9%). Twenty-third treatment: amount: 1000 cc.; rise on the right side on inspiration 7.3 cm. (32.8%), on expiration 5.8 cm. (30.2%); on left side on inspiration 5.4 cm. (22.9%), on expiration 5.6 cm. (21.7% of the apico-basal diameter).

These cases demonstrate that a substantial and sustained elevation of the diaphragm, and consequently a satisfactory relaxation of the lung, can be produced by weekly injections of air into the peritoneal cavity.

Summary. 1. Comparative measurements and analysis of 264 roentgenograms of the chest, taken before and during artificial pneumoperitoneum treatment of 40 patients, are presented. These data and their evaluation must be interpreted with the qualification that it was impossible to eliminate entirely some differences in the respiratory efforts of the patients, and consequently in the motion of the chest and the diaphragm, when films were taken on repeated occasions.

2. Repeated injections of air into the peritoneal cavity at weekly intervals are likely to cause a sustained elevation of the diaphragm, provided, pathologic changes, such as fixation of the diaphragm by adhesions, or the presence of extensive adhesions between the

convexity of the liver and the lower surface of the diaphragm, do not obviate it.

3. The maximum elevation of the diaphragm induced by pneumoperitoneum was on inspiration 7.3 cm. on the right side and 6.4 cm. on the left side; on expiration 6.4 cm. on both sides.

4. The maximum elevation of the diaphragm by pneumoperitoneum was greater than that observed after surgical paralysis of the phrenic nerve in a comparable group of patients.

5. The maximum reduction in the length of the apico-basal diameter was on inspiration 32.8% on the right side and 27% on the left side, and on expiration 32.6% on the right side and 34.3% on the left side.

Conclusion. Artificial pneumoperitoneum treatment in pulmonary tuberculosis, when given at regular intervals, is capable of inducing a degree of relaxation of the lung that is known to be sufficient to improve the resistance, defense, and repair of the pulmonary tissues, and thus it brings about a condition which is favorable to the healing process of tuberculous lesions.

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DIABETIC COMA REQUIRING AN UNPRECEDENTED AMOUNT OF INSULIN.

Report of a Case Manifesting Extreme Insulin Resistance.

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The case of atypical diabetes mellitus described in this preliminary report was rescued from coma by means of the administration of larger doses of insulin than appear ever to have been given before. The subsequent clinical course in the 5 months to date (January 31, 1938) has been featured by the continued need for daily administration of very large doses of insulin. The largest dose given in 24 hours, on September 27, 1937, was 3250 units of regular insulin, which, I believe, according to a search of the literature, is by far the largest amount ever given to a human subject.

Report of Case. Mr. J. S., Jewish, born in Russia in 1879, first seen September 21, 1937, at the age of 58, is a grocery-store owner who has lived in New York City for the past 31 years. He is married and has

4 children who are living and well. As far as he knows no other member of his family has had diabetes. There was no serious medical or surgical illness in his past history.

At an insurance examination in 1934 a trace of sugar was found in the urine. At that time he weighed 160 pounds. Early in the winter of 1937 symptoms of moderately severe diabetes gradually developed, *viz:* polyuria, polydypsia and polyphagia. However, as he neglected to seek medical advice, no diagnosis was made or treatment instituted up to the time of hospitalization.

Two days before his first admission to the Gouverneur Hospital on May 14, 1937, the patient complained of a pain in the right groin, and of

FIG. 1.—Mr. J. S., January 20, 1938.

FIG. 2.—Mr. J. S., January 20, 1938.

dysuria. His temperature was found to be 101° F.; the urine showed a few pus cells, 3% of sugar and 2+ acetone. The blood sugar was then 425 mg. %; N.P.N., 27. On admission, his weight was 131 pounds; there was slight costo-vertebral tenderness, and temperature 101° F. The tentative diagnosis was pyelitis. Regular insulin in diminishing doses, starting at 155 units in the first 24 hours, brought the diabetes under control in 1 week, and he was discharged after a 2 weeks' stay in the hospital with the urine free of sugar and acetone and on protamine-zinc insulin, 50 units

in 1 daily dose. The diet on discharge was: C., 200; P., 70; F., 70. His weight was 129 pounds. During the summer he gained weight up to 140 pounds and remained sugar-free on this régime.

Three weeks previous to his second admission on September 13, 1937, a large amount of sugar was again found in the urine, although the patient insists that there had been no "breaks" in his diet. The diet was then further restricted and protamine insulin gradually increased, with the addition of a certain amount of regular insulin, but at the end of a week the sugar had not decreased, and acetone 2+ had appeared in the urine. He was then kept in bed at home for 2 weeks; fluids were forced, and regular insulin was gradually increased up to 260 units in divided doses without any signs of improvement. His weight dropped to 110 pounds in a period of 4 weeks. On the night before readmission, September 14, 1937, clinical signs of marked acidosis were evident, including acetone odor to the breath and marked hyperpnea. He complained that night of severe substernal burning sensation, and vomited once.

Physical examination at the hospital was essentially normal for a man of his age, except for the marked dehydration and the evidences of acidosis. There was no abnormal pigmentation of the skin or mucous membranes, nor any obvious adenopathy. The heart and lungs were normal. The peripheral arteries were moderately thickened and slightly tortuous. There was visceroptosis. The liver was not enlarged but the edge could be felt due to ptosis. There was no evidence of the presence of any abnormal abdominal masses or of ascites. All superficial reflexes were normal. There was no edema of the extremities or elsewhere. The eyegrounds were normal except for evidence of moderate arteriosclerosis. The visual fields were normal. Roentgen ray films of the skull and the chest revealed nothing abnormal. The renal function was apparently entirely normal. Blood sugar was 344 mg. % and CO_2-combining power of the plasma, 29 vol. %. The routine treatment for pre-coma was instituted, and 440 units of insulin given in the first 24 hours. Fluids in the amount of 8000 cc. were given and the output was 5000 cc. On the next day 1105 units of insulin were given, carbohydrates of about 200 gm.—part by 5% glucose infusion—but the sugar remained 4+ in the urine (6800 cc.) although acetone was absent. During the next 5 days excessive polyuria, high glycosuria, and increasing ketonuria persisted, despite an average daily dose of 900 units, and subjective and objective signs of incipient coma were definitely present on September 21, 1937, when I first saw the patient. Although the CO_2 was 54 on September 17, on September 21 at 8 A.M. it had fallen to 9, and at 12 M., due to the measures instituted, as shown in Table 1, the CO_2 rose to 19.

The essential data of the critical 24 hours from 8 A.M. September 21 to 8 A.M. September 22 will be found in Table 1. It will be noted that glycosuria was controlled, ketonuria diminished, and the clinical condition markedly improved, chiefly due to 5 measures: 1, Very large and frequently repeated doses of insulin;* 2, large amounts of fluid; 3, alkali (sodium bicarbonate); 4, sodium chloride, by vein; 5, cardiac and respiratory specific stimulation.

The essentials of the daily record through October 20, 1937, may be found in Table 3, and it will be noted that the largest dose of insulin was given September 27 to 28, 1937. The details of this single day are shown on Table 2. The reason for administering this large amount was that the

* Through the obliging coöperation of the New York office of Eli Lilly and Company, several thousand units of their U–100 regular insulin were supplied gratis to the patient during the first 2 weeks, and since then E. R. Squibb & Co. have donated from 10,000 to 14,000 units of their U–100 regular insulin every week for 12 weeks, a total to date of 142,000 units.

patient had again begun to show ketonuria as well as the clinical signs of acidosis, despite the large doses of insulin given on the preceding days. He has shown no signs of acidosis since that day (except on one occasion a month later) and was subjectively well and up and about the ward, and discharged, November 5, 1937. He was instructed to take 1700 units of insulin, divided into 4 doses, and a diet of C., 300; P., 100; F., 100. He has since been managed as an ambulant patient, and has been working at his regular occupation.

TABLE 1.—CLINICAL COURSE ON SEPTEMBER 21 AND 22, 1937.

Time.	Insulin, units.	Blood chemistry.		Urine.			Remarks.
		Sugar, mg.%.	CO_2, vol.%.	Vol., cc.	Sugar, %.	Acetone.	
Sept. 21.							
12.01 A.M.	**100**	...	...	310	4.0	4+	P., 112; R., 26; acetone on breath, 4+—*all day.*
2.00 A.M.	100	...	...	220	2.0	3+	
6.00 A.M.	100	...	...	200	3.0	3+	Vomited; B.P., 140/80.
8.00 A.M.	...	242	9	...	...	...	Stuporous.
10.00 A.M.	50	...	...	120	3.5	4+	N.P.N., 26.
12.00 M.	...	238	19	...	...	...	Infusions, 500 cc. 5% $NaHCO_3$ and 5% NaCl; at 11.20 A.M., P., 128; B.P., 90/60; R., 22.
1.00 P.M.	150	...	...	780	4+	4+	Insulin given in 1000 cc. of 5% glucose and physiologic saline.
2.00 P.M.	**100**	...	...	520	4+	4+	Strophanthin, 0.75 mg. IV at 1.45 P.M.
2.45 P.M.	100						
4.00 P.M.	...	...	...	360	4+	4+	Metrazol, 2 cc. IM.
6.00 P.M.	...	...	...	360	4+	4+	Metrazol, 1 cc. IM at 5 and 6 P.M. Strophanthin, 0.75 mg. IV at 4 and 6 P.M. Still drowsy; condition unchanged; R., 38.
6.45 P.M.	...	...	...	320	4+	4+	Infusion, 500 cc. 5% $NaHCO_3$ at 6.30 P.M.
8.00 P.M.	200	...	...	300	4+	4+	Infusion, 200 cc. 5% glucose.
9.00 P.M.	200	...	...	300	4+	4+	
9.30 P.M.	... *	...	...	320	4+	4+	
10.00 P.M.	200	...	...	240	4+	4+	
11.00 P.M.	200	...	...	450	4+	4+	4 gm. $NaHCO_3$ by mouth at 10.45 P.M.
	1500	...	...	4900	...	...	Total for 24 hours.
Sept. 22							
12.00 M.	200	...	...	180	4+	4+	Restless; respirations labored.
1.00 A.M.	200	...	...	450	4+	4+	
2.00 A.M.	200	...	...	360	2.0	4+	
3.00 A.M.	200	...	...	180	1.8	4+	
4.00 A.M.	200 *	...	...	160	1.5	4+	
5.00 A.M.	200	...	...	180	1.0	4+	
6.00 A.M.	200	...	...	120	0.5	4+	
6.30 A.M.	200	...	...	120	0.4	3+	Infusions, 500 cc. 10% glucose.
7.00 A.M.	...	...	...	50	Tr.	2+	Condition better, respirations normal.
8.00 A.M.	...	...	...	30	Tr.	2+	Color fair.

Antique figures represent protamine zinc insulin.
* 1800 cc. of normal saline 9 P.M. to 8 A.M. given very slowly by vein and containing all subsequent insulin. Metrazol, 1 cc. IM at 7 and 8 P.M. B.P., 112/50.

The insulin was increased to 2800 units on November 24, 1937, because of ketonuria and symptoms of acidosis on the preceding day on a dosage of 2000 units. This was then reduced on November 26, 1937 to 1400 units in 5 doses.

On December 6, 1937, he took regular insulin as follows: 6 A.M., 600 units; 8 A.M., 400; 11 A.M., 400; 2 P.M., 200; 5 P.M., 200; 8 P.M., 200; 10 P.M., 200. And this was his insulin régime throughout December and the first 2 weeks of January, except for minor variations in dosage. With the diet

remaining the same, the 24-hour urinary sugar would vary from 40 to 90 gm. At the present time he is excreting about 50 gm. and the insulin has been reduced to 700 units, with the following dosage: 6 A.M., 300, and subsequent 4 doses of 100 units Q.4H. up to 10 P.M. His present weight is 142 pounds and he is subjectively entirely well.

The patient was in the Post-Graduate Hospital for a 48-hour period of observation (January 27 to 29). The diet was carefully controlled at C., 300; P., 100; F., 100; and the insulin, 1400 units, given in the same intervals and amounts as he had been taking outside. Table 4 shows the analyses of the divided urine specimens and other relevant data. The

TABLE 2.—CLINICAL COURSE ON SEPTEMBER 27, 1937.

Time.	Insulin.		Urine.				Remarks
	Units.	Route.	Vol., cc.	Sugar, %.	Sugar, gm.	Acetone.	
Sept. 27							
9 A.M.	...	...	330	2.0	6.6	0	Bl. sugar, 185; CO_2, 59; Cl., 420; N.P.N., 27
10 A.M.	250	SC	390	2.4	9.5	0	5 gm. $NaHCO_3$ by mouth, 1 gm. NaCl by mouth.
11 A.M.	...	...	210	3.0	6.3	Tr.	
12 M.	150	SC	300	1.4	5.2	Tr.	1 gm. NaCl by mouth.
1 P.M.	150	SC	300	2.0	6.0	Tr.	
2 P.M.	150	SC	150	2.0	3.0	1+	1 gm. NaCl by mouth.
3 P.M.	150	SC	210	3.3	6.6	Tr.	
4 P.M.	150	SC	270	3.5	9.7	1+	1 gm. NaCl by mouth.
5 P.M.	150	IV	240	3.3	8.2	1+	2 gm. NaCl by mouth.
6 P.M.	150	IV	210	2.8	6.0	1+	1 gm. NaCl by mouth.
7 P.M.	150	IV	120	1.8	3.6	1+	
8 P.M.	150	IV	120	1.9	2.3	Tr.	
9 P.M.	150	SC	150	1.0	1.5	Tr.	
10 P.M.	250	IM	120	0.5	0.6	Tr.	NOTE.—Last day of ketonuria.
11 P.M.	...	...	100	0.2	0.2	0	Patient subjectively well.
12 M.	250	IM	125	0.4	0.5	0	Diet: C., 180; P., 120; F., 60;
1 A.M.	...	...	120	0.8	1.0	0	divided in 6 meals at 6 A.M.,
2 A.M.	250	IM	300	0.3	0.9	0	10 A.M., 2 P.M., 6 P.M., 10 P.M.,
3 A.M.	...	...	120	0.4	0.5	0	2 A.M.
4 A.M.	250	IM	100	0.5	0.5	0	
6 A.M.	250	IM	300	0.1	0.3	0	
8 A.M.	250	SC	200	0.7	1.4	0	
	3250	...	4485	...	82.0	...	Total in 24 hours.
Sept. 28							
9 A.M.	...	...	...	...	...	...	Bl. sugar, 66; CO_2, 46.

highest concentration of glucose in the urine is seen to occur between the hours of 7 and 11 A.M. Although there never have been any clinical indications of hyperthyroidism, the basal metabolic rate was 29% above normal.

An attempt was made to determine whether the presence of contra-insulin hormones could be detected in the patient's blood. To this end the serum of the patient and the serum of a non-diabetic case were incubated with insulin for 3 days, and then injected intravenously into fasting rabbits and the blood sugar lowering effect studied. As seen in Table 5, the serum of the patient in this test manifested no contra-insulin activity.

The possible presence of insulin antibodies in the serum of the patient was ruled out by Prausnitz-Kustner passive transfer tests, done by Dr. M. B. Sulzberger and his co-workers. These experiments were performed with ordinary purchasable insulin, as well as with the special pork and the special beef insulins of Lilly. The results proved that there were no passive transfer antibodies to insulin in the serum of the patient.

With the coöperation of Dr. M. Bruger and Dr. C. V. Bailey, a detailed metabolic study was undertaken at the Post-Graduate Hospital, the results of which will be published in a subsequent communication.

TABLE 3.—CLINICAL COURSE IN SEPTEMBER AND OCTOBER.

Date.	Insulin, units in 24 hrs.	Blood chemistry.			Urine.			Remarks.
		Time.	Sugar, mg. %.	CO_2, vol. %.	Vol., cc.	Sugar, gm.	Ketones.	
Sept.								
13	425	...	...	...	...	...	4+	B.P., 160/80.
14–16	1560 (45 hr.)	...	375	...	...	...	4+	
16	1105	...	161	...	3000	12	4+	
17	715	...	225	54				
20	785	...	...	...	...	(2–4%)	4+	Blood Cl., 420
21	1500	8 A.M.	242	9	5000	225	4+	B.P., 90/60; acetone breath, 4+; P., 120–130.
		12 M.	238	19	...	...	...	Cl., 60 gm.; $NaHCO_3$, 83 gm. by mouth *et seq.*
22	2700	9 A.M. 1 P.M.	153	30 35	3000	30	Tr.	Blood acetone, 78 mg. % with urine acetone negative.
23	1220	...	200	64	3800	40	Tr.	Diet: C., 180; P., 120; F., 60; in 6 meals; B.P., 140/80.
24	2200	...	217	63	5500	77	Tr.	Urine Cl. in 24 hours, 10 gm.
25	1620	...	200	54	5500	150		
26	2440	1 P.M.	222	36	4500	90	0	
27	3250	8 A.M.	185	59	4300	40	0	Urine Cl. in 24 hours, 8 gm.
28	1200	9 A.M.	66	46	2400	12	0	First mild insulin reaction, 2 P.M.
		2 P.M.	75	...	...	...	...	Second mild insulin reaction, 6 P.M.
29	1800	...	224	51	2400	14	0	
30	2100	...	127	...	3200	100	0	Calcium gluconate begun.
Oct.								
1	1700	...	...	...	2450	24	0	
2	1450	...	222	39	2400	25	0	
2	1300	...	...	...	1800	50	0	
4	1300	...	...	...	1500	78	0	
5	1300	...	...	...	2000	40	0	Diet: C., 260; P., 80; F., 100 mild ins. reac.
6	1200	...	...	...	2500	13	0	Diet: C., 300; P., 100; F., 100
11	1420	...	247	53	1800	45	0	
15	1620	1 P.M.	125	54	1930	38	0	Bl. Cl., 440; chol., 174; Ca., 10.4; P., 4.4.
18	1600	11 A.M.	280	...	1960	100	0	Bl. Cl., 515; pl. Cl., 645; uric ac., 3.2.
19	1660	2 P.M.	283	...	2000	68	0	No insulin reaction since Oct. 15.
20	...	...	...	...	2160	75	0	

TABLE 4.—TWO-DAY OBSERVATION AS IN-PATIENT IN DECEMBER.

1937.	Time of collection.	Vol., cc.	Specific gravity.	Sugar.		Acetone.	Insulin.	Diet.
				%	Gm.			
Dec. 27	7 P.M.–							
28	7 A.M.	382	1.023	1.2	4.6	0		
	7 A.M.–11 A.M.	856	1.025	6.7	57.3	Tr.	1400 units in 7 doses	C., 300; P., 100; F., 100.
	11 A.M.– 3 P.M.	235	1.028	5.6	13.2	Tr.		
	3 P.M.– 7 P.M.	320	1.028	4.0	12.8	Tr.		
	24 hours	1793			87.9			
29	7 A.M.– 9 A.M.	135	...	6.0	8.1			

Dec. 28: Insulin, SQ, 500 units at 6 A.M., 300 at 8 A.M., 200 at 10 A.M., and 100 at 1, 4, 7 and 10 P.M.

Dec. 29: B.M.R., +29%; pulse, 88; fasting blood sugar, 306 mg. %.

TABLE 5.—TEST FOR CONTRA-INSULIN ACTIVITY OF SERUMS.

(4.5 cc. serum to which was added 0.5 cc. Insulin U-40 (20 units), incubated for 3 days at 37° C. These sera were then injected intravenously into 2 fasting rabbits and blood sugars done fasting, and at ½-hour, 1 hour and 2 hours after injection.)

Fasting.	J. S., aet 58. Rabbit I. 106 mg. %.	Non-diabetic male, aet. 54. Rabbit II. 100 mg. %.
½ hour	86	74
1 hour	66	76
2 hours	48	66

Summary. This case represents an extreme degree of insulin resistance, in a patient whose diabetes mellitus was in other respects unremarkable. As high as 3250 units were given in 24 hours. Our experience in the critical period of coma indicates that very large doses of insulin may be required to save the life of the exceptional case. Further research is being undertaken with this patient in an attempt to uncover the fundamental factors underlying his insulin resistance.*

* The patient on July 26, 1938, is clinically well, the insulin dosage having been reduced to 440 units daily. On July 20 the 11-A.M. blood sugar was 138 mg. % and the urine at that time contained 1.8% glucose (glucose excretion about 15 gm. daily). Further evidence of the absence of a diabetogenic hormone of anterior pituitary origin has very kindly been furnished by Prof. C. N. H. Long, of Yale (June, 1938), who injected precipitates from the patient's blood and urine over 3 days to partially depancreatized rats known to be susceptible to anterior pituitary extract, with no effect on the glycosuria of these animals.

HYPERINSULINISM AND PREGNANCY.

REPORT OF A CASE.

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A CAREFUL search of the literature fails to reveal a single reported case of coëxisting hyperinsulinism and pregnancy, though 2 somewhat similar cases have been recorded. Schwarz[18] reported a case of hypoglycemia in pregnancy, but in his patient there was an associated hyperthyroidism and the hypoglycemia occurred late in gestation. John[13] reports a case of hyperinsulinism, successfully treated with insulin, in which, 2 years after recovery, normal pregnancy with delivery of a normal child occurred. No other reports of children born of hypoglycemic or hyperinsulinic mothers appear to have been made. The following case, therefore, is of special interest and should be on record.

Case Report. L. H., a white female, was married in 1920 at the age of 20. In 1921, labor was induced during the 8th month of her first pregnancy because of nephritic toxemia. In 1923, her husband's suicide precipitated a serious emotional disturbance which continued during the next 2 years.

In 1925, the patient married a brother of her first husband. In March, 1926, her second pregnancy ended spontaneously at 3½ months. In December, 1926, her third pregnancy terminated spontaneously at 3½ months with profuse hemorrhage.

In 1930, menstruation, which hitherto had been normal, recurring every 28 days and lasting 6 days, rapidly decreased to a flow of ½ to 1½ days. In 1931, the patient first came to me for treatment complaining of continual nervousness, with exacerbations consisting of irritability, weeping and depression. Examination was totally negative except that the patient appeared undernourished. Her weight was 93 pounds (42 kilo.) and her height 62 inches (157 cm.).

During the winter of 1931–32 there were numerous menstrual delays of from 6 weeks to 2 months. In 1932, there appeared occasional severe attacks of nausea and vomiting, each lasting 2 to 3 days, together with marked anorexia that persisted thereafter. During 1933, the menstrual irregularity and unrelated attacks of nausea and vomiting continued. For

about a month, beginning in May, 1934, the patient had recurrent evening fever, the temperature rising to between 99.5 and 100.5° F. and being irregularly associated with dyspnea, palpitation, nausea and fatigue. The patient was exhaustively studied at this time with totally negative results.

In October, 1934, she developed griping pain in the epigastrium, occurring shortly after arising in the morning and persisting for about 1 hour. This was followed by soreness at the site of the pain, belching and nausea. Examination revealed only epigastric tenderness. Attacks began to appear in the late afternoon, associated with fatigue, vertigo and faintness. They also occurred during the night, but less frequently. When I saw the patient in a severe attack one morning in November, 1934, she presented a picture strongly resembling that of overdosage of insulin. There was marked pallor, a cold clammy sweat, the pupils were widely dilated, and there were generalized tremors and facial twitchings. Speech was thick and somewhat unintelligible. The patient complained of severe epigastric pain, vertigo, and diplopia. These symptoms abated promptly when the patient was given sugar and orange juice. A glucose tolerance test done during the next week showed a flat curve (Chart 1). This was interpreted as being

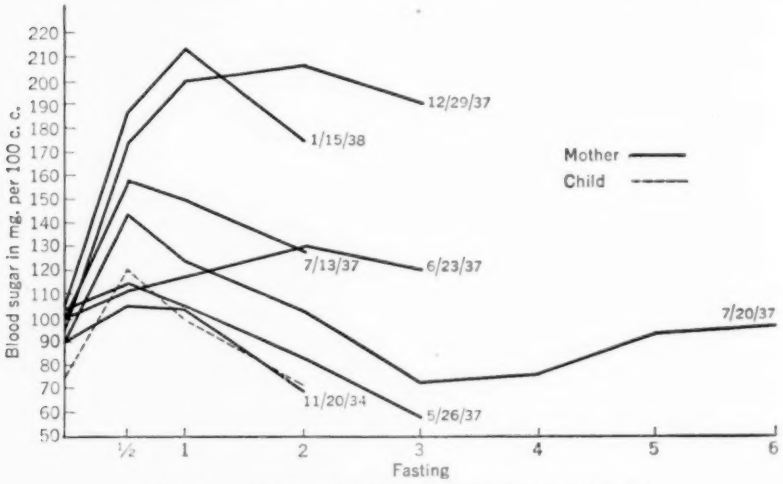

CHART 1.—Glucose tolerance tests on mother and child.

indicative of hyperinsulinism, although none of the specimens showed a marked hypoglycemia. When the patient began to take small amounts of food regularly between meals and on retiring, recurrence of her hypoglycemic symptoms were largely avoided.

During the first 5 months of 1935 the hypoglycemic attacks were under fair control. The menstrual irregularity became marked by increasingly frequent intervals of amenorrhea and progressively diminishing amount of flow, the catamenia now lasting only one-half day. Mental depression increased steadily. From June, 1935, she gradually became addicted to alcohol until she was taking as much as 16 to 20 ounces of whiskey in the course of an evening. In December, 1935, epigastric pain and vomiting reappeared. Several months of treatment with diet, psychotherapy and large doses of anterior pituitary-like sex hormone failed to bring about any improvement. In September, 1936, her tolerance for alcohol diminished rapidly and there was an increasing maniacal tendency, evidenced by fits of inexplicable rage

and unmanageability. Otherwise, the patient continued quite depressed, had persistent nausea and vomiting, marked anorexia and insomnia. Insulin therapy, as suggested by John,[13] had to be promptly abandoned because as little as 5 units produced marked shock.

Early in November, 1936, nausea and vomiting became more pronounced. Because the patient had menstruated last on September 25, 1936, an Aschheim-Zondek test was done and proved positive for pregnancy. Announcement of this fact proved of great benefit to the patient, bringing about a prompt decrease in her symptoms. Vomiting persisted until the 10th week, insomnia and nausea until the 16th week when the patient was restored to a full diet with carbohydrate feedings between meals because of marked afternoon fatigue. In the 29th week (April 19, 1937) nausea and faintness began to occur at 3 A.M., waking the patient. Orange juice and sugar relieved these symptoms which subsided during the final 3 weeks of the pregnancy. A 3 A.M. specimen and 1 at 4 P.M. taken during the 34th week showed 67 mg. and 87 mg. of sugar per 100 cc. of blood respectively. A glucose tolerance test on May 26, 1937, showed a flat curve; another on on June 23, 1937, revealed a moderate decrease in tolerance. Blood pressure and urine remained normal throughout the pregnancy. The weight gain was interesting. By the 27th week (Apr. 10, 1937) it had reached 118½ pounds and it remained at this level, about 24 pounds above the patient's usual weight, until term. After the 27th week, while the abdomen continued to enlarge, the patient definitely lost flesh about the face and extremities.

The fetus, which was first felt at 19 weeks (Feb. 2, 1937), was unusually active. Pregnancy ended on July 4, 1937, at full term. During labor, which lasted 7 hours, hypoglycemic symptoms occurred twice. The child was born spontaneously on July 4, 1937. The mother's blood sugar examined immediately after the end of the second stage of labor showed 107 mg. per 100 cc.

The puerperium was uneventful. Marked hypoglycemic symptoms which occurred during the first 3 days ceased after the patient was placed on a high fat-low carbohydrate diet[13] made up of 60 gm. of protein, 90 gm. of carbohydrate and 180 gm. of fat. On this diet the patient gained weight. A glucose tolerance test on July 13, 1937, showed a definite decrease in tolerance; another on July 20 showed a slight increase.

The patient menstruated for the first time postpartum on Sept. 25, 1937, and again on Oct. 22, 1937, both periods being of 7 days' duration and of good volume. She felt and acted normally in all respects. In early November there was a recurrence of nausea, severe headache and backache, anorexia, insomnia and mental depression. There have been no further symptoms of hypoglycemia. Menstruation in November and December, 1937, was delayed, brief, and scanty. Glucose tolerance was found to be markedly reduced. Institution of insulin therapy (5 units 3 times daily) has resulted in marked remission of all symptoms with tendency to only very mild insulin reactions.

Insulin therapy was begun on January 17, 1938. The first subsequent menstruation occurred January 28 to 31, with a freer flow than in November and December, 1937. Menstruation in February to May, 1938, inclusive, has in each instance been of 3 to 4 days' duration, of normal volume, and only slightly delayed.

The patient has had mild acne rosacea for about 15 years. This condition improved very greatly during the last pregnancy but recurred in severe form in November, 1937, with the return of menstrual and mental symptoms. On institution of insulin therapy the acne improved almost to the point of total disappearance and has since shown mild exacerbations only immediately preceding menstruation. This observation is in accord

with that of Wortis[21] in the insulin hypoglycemia treatment of dementia præcox patients who also had acne vulgaris.

The child, a normal female, weighed 6 pounds and 2 ounces at birth. Her venous blood sugar 72 hours after birth was 71 mg. per 100 cc. of blood. There has been no symptomatic evidence of hyperglycemia or hypoglycemia. Several urine specimens have been negative for sugar. At the time of this report development, including dentition, nutrition, mentality and growth, has been normal. Repeated glucose tolerance studies have shown the normally flat curve characteristic of infants (Chart 1).

Discussion.—The etiologic considerations in this case are as important as they are interesting. The comparatively mild symptoms would place this patient in the group of relative or secondary hyperinsulinism. The primary endocrine dysfunction appears to be in the pituitary gland. While Simmonds' disease presents itself for consideration, most of the characteristic features of pituitary cachexia are not evident in this case. The so-called functional cases of chronic hypoglycemia tend to display a flat glucose tolerance curve.[1] The present case repeatedly showed such curves.

The existence of such an entity as hyperinsulinism was postulated by drawing a parallel between the pancreas and the thyroid gland.[2,11,19] Psychic trauma, a possible etiologic factor in exophthamic goiter, might reasonably also be a factor in relative hyperinsulinism. A violent psychic disturbance occurred in my patient and its rôle, directly or indirectly, in the etiology of the disturbance of insular function is at least probable. The mechanism of the influence of psychic trauma in hyperthyroidism and hyperinsulinism is uncertain. Experimental studies indicate that the higher nervous centers take part in the regulation of insular secretion through the vagus.[3,22a] Disturbances in function may take place through the mediation of other glands. There is experimental evidence that the pituitary gland acts on the pancreas to increase insulin output both directly and through the thyroid gland.[22b] Prolonged perversion of function may conceivably induce organic changes in the form of hypertrophy and hyperplasia. It is possible that the more severe cases of hyperinsulinism associated with hyperplastic and hypertrophic changes in the Islands of Langerhans (but excluding tumors of the islands) represent the ultimate result of perversion of function caused by endocrine disturbances in other glands. This would account for earlier or milder cases of hyperinsulinism without demonstrable pancreatic disease. It would explain also the failure of partial resection of the pancreas to abolish symptoms of hyperinsulinism in some cases.

The menstrual disturbances in the present case were related to and probably secondary to the hyperinsulinism. There is ample proof that irregularities in insulin secretion produce similar irregularities in menstruation.[4,5,14,20]

Reports indicate an increased functional activity of the Islands of Langerhans during pregnancy, particularly during the middle period

and toward the end of gestation, followed by gradual decrease just before parturition.[8,17] In the present case, hypoglycemic symptoms were more marked between the twenty-ninth and thirty-seventh weeks of pregnancy. The glucose tolerance studies show that tolerance began to decrease in the final weeks of pregnancy and continued to decrease after parturition. An attempt made to increase the glucose tolerance by restoring the patient to a high carbohydrate

TABLE 1.—GLUCOSE TOLERANCE TESTS ON MOTHER AND CHILD.

	Mother.							Child.		
Time.	11/20/34.	5/26/37.	6/23/37.	7/13/37.	7/20/37.	12/29/37.	1/15/38.	1/12/38.	2/2/38.	2/21/38.
Fast	92	104	100	100	91	96	107	80	77	76
½ hr.	105	115	112	158	143	176	188	116	120	117
1 hr.	104	104	118	150	125	200	214	80	100	93
2 hr.	70	84	130	128	103	206	176	72	71	82
3 hr.	...	57	121	...	73	192				
4 hr.	...	...	...	...	77					
5 hr.	...	...	...	...	94					
6 hr.	...	...	...	...	96					

All urine specimens in all tests were negative for sugar; 1.75 gm. glucose per kilo in all tolerance tests.

diet for 1 week preceding the final curve[12a,b] seemed to have only slight effect. One may conclude that pregnancy favorably influenced the hyperinsulinism in this case. The reasons for this improvement are uncertain. They may depend on the widespread alteration in function of all the endocrine glands, ordinarily present in normal pregnancy, with secondary changes in pancreatic function. They may depend on insulin relationship between fetus and mother. Increasingly numerous reports of children with hyperinsulinism born of diabetic mothers,[6,7,9,10] as well as reports of children with thyroid enlargement born of hypothyroid mothers[16] and of cretins born of mothers with exophthalmic goiter[15,16] point strongly to an interchange of endocrine substances between fetus and mother. A transfer of insulin from fetus to mother would depress maternal pancreatic function. Experimental and clinical evidence indicates that injections of insulin reduce activity of the Islands of Langerhans.[13,21c] In the present case fetal insulin may have been the equivalent of injected insulin in depressing maternal pancreatic islet function. The improvement of the hyperinsulinism in this case, if due to general maternal endocrine changes of pregnancy or to fetal influences, would obviously be temporary.

The endocrine relationship between fetus and mother as cited above has in no demonstrable manner affected the child in this case. There is no evidence of diabetes or hyperinsulinism in the child. To date development has been normal in all respects.

Summary.—1. A case of hyperinsulinism and pregnancy with successful delivery is herein reported.

2. The pregnancy appears to have lessened the hyperinsulinism in the mother, reducing the sugar tolerance.

3. The child is normal in all respects.

4. The possible etiology of the hyperinsulinism in this case is discussed. In addition to accepted causes, psychic trauma, as noted in this case, appears to be a probable cause.

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UVEO-PAROTID FEVER (HEERFORDT'S SYNDROME) NEUROLOGIC MANIFESTATIONS.

REPORT OF TWO CASES.

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UVEO-PAROTID fever is either rarely encountered in the practice of most physicians or else the syndrome is mistakenly diagnosed as some other disease. Most standard textbooks on medicine fail to make any mention of this condition, yet the similarity in cases thus far reported unquestionably justifies its classification as a separate clinical entity. Uveo-parotid fever may be defined as a comparatively rare affection, characterized by inflammatory lesions of the uveal tract, a bilateral almost painless enlargement of the parotid glands, a low grade chronic fever, subject to many variations and by the occurrence of irregular constitutional symptoms. Paralysis of cerebrospinal nerves, particularly the facial nerves, occurs frequently. The majority of the patients have been in the second and third decades of life, although it may occur at any age. It is somewhat more prevalent in females, of the white race, though several cases among negroes have been recorded.

Uveo-parotid fever, as a clinical syndrome, was first recognized and described by the ophthalmologist Heerfordt,[11] of Copenhagen, in 1909. Under the name "Febris uveo parotidea subchronica," he reported 3 cases and discussed 2 others with similar clinical features, and expressed the belief that this disease was an atypical form of mumps. Merrill and Oaks[19] reviewed the literature up to 1931, and Garland and Thomson,[9] in a very comprehensive study, summarized 47 cases from the literature in 1933. More recently, Levin[15] analyzed 66 cases, from the neurologic standpoint.

Case Reports. CASE 1.—Patient M.D. (Fig. 1), a 22-year-old negro housewife, was admitted to this hospital on November 3, 1937, complaining

FIG. 1.—Case 1. Three weeks after admission, shows some enlargement of the parotid glands and ptosis of the eyelids. Note the skin eruption on the face.

of fatigue, lassitude and malaise of 5 months' duration, drooping of the eyelids, and swellings at the angles of the jaws. The swelling of the left side of the face was present for 6 weeks and that on the right for 3 weeks. At the onset of her illness, she complained of a slight pain in the left side of the face. She had been nearsighted for many years, but spots appeared before her eyes and she was unable to see distinctly for 3 weeks prior to her admission. She was drowsy and very thirsty, drinking up to a gallon of water daily. Rinsing the mouth with water did not relieve her thirst. She lost 8 pounds in weight within 3 months. There was no history of skin eruptions and her menses were regular. Her past history revealed that at the age of 14 years, she was confined for 8 months to an institution, because of an incipient tuberculosis. The family history disclosed tuberculosis as the cause of death of both her mother and father. She has 3 brothers and 1 sister, but has no knowledge of their whereabouts or health. She has 3 healthy children.

General Medical Examination. The patient was an intelligent, young colored female and not acutely ill. Several small, shotty glands were palpable in the cervical region. Both parotid glands were enlarged, the left somewhat more so than the right. The enlargement was diffuse and more marked over the preauricular portions. The other salivary glands as well as the lachrymal glands were not enlarged. Stenson's ducts were not pouting or inflamed. The other findings were essentially negative. The blood pressure was 110/84. Neurologic examination: The gait and station were not tested because she was in bed with a temperature of 101° F. The pupils were in mid-dilatation, equal and reacted promptly to light and in accommodation. The left pupil was slightly irregular and there was some difficulty in convergence in the right eye. Leukomata were noted on both corneas, and the anterior chambers were distinctly deepened. The fundi oculi and perimetric visual fields were within normal limits, but her visual acuity was considerably reduced (20/200). Ocular tension, O.D., 18; O.S., 20. Bilateral ptosis of the eyelids with a tendency to chronic wrinkling of the forehead were noted. The other cranial nerves, grossly tested, were intact. The upper deep reflexes were present and equally active. The right knee jerk was more active than the left. The abdominal reflexes were present and equal. On plantar stimulation there was a prompt flexor response on the right, but none on the left. Sensory examination was normal to all modalities.

Laboratory Findings. Urine: Specific gravity, 1006 (on 2 concentration tests). No abnormal constituents were found. The daily fluid intake in ounces ranged from 147 to 196 and the output from 192 to 129. Pituitrin given intramuscularly reduced the intake and output by about 50% but had to be discontinued after 3 days because of the complaint of severe headache. Blood: Hemoglobin, 70; leukocytes, 11,200; neutrophils, 68; lymphocytes, 32; erythrocytes, 3,800,000. Chemistry (in mg. per 100 cc. of blood): Sugar, 120; urea nitrogen, 14; creatinine, 1; total protein, 8%; albumin, 5%; globulin, 2.6%. Wassermann test, negative. Spinal fluid: initial pressure 150 mm. of water, clear, colorless, no cells, total protein 0.22 mg. %, No evidence of block. Wassermann and colloidal gold tests were negative. Mantoux tuberculin test was negative. Basal metabolism was −18. An aspiration of the parotid gland was attempted but insufficient material was obtained for microscopic study. A biopsy of the parotid was refused. Electrocardiographic tracings showed a depressed T wave in Lead II and an inverted and coved T wave in Lead III, suggestive of cardiac involvement. Roentgen ray studies were made at various intervals and reported by Dr. Samuel Weitzner. A chest plate taken on Dec. 30, 1936 (Fig. 2), showed no abnormality. On Nov. 5, 1937, another film (Fig. 3) disclosed a distinct and marked enlargement of the glands at both lung roots. On Nov. 30, 1937, a radiograph of the chest revealed a marked enlargement of the glands at both lung roots and scattered throughout both lungs were small, punctate areas of infiltration, but no evidence of pleural effusion (Fig. 4). Roentgen rays of the mandible and supramandibular regions showed no evidence of calculi in the salivary glands. Roentgenograms of the skull, including the sella turcica, and of the long bones were negative.

Course. During her stay in the hospital the swelling of the parotid glands gradually diminished and upon her discharge on Dec. 14, 1937, there was practically no enlargement visible or palpable. No change was noted in the eyes, but the bilateral ptosis had improved considerably. It is interesting to note that the water intake and output was diminished for several days following the injections of pituitrin. This began with the third injection and continued for 3 days after the medication had been discontinued. The temperature was within normal range during most of her stay.

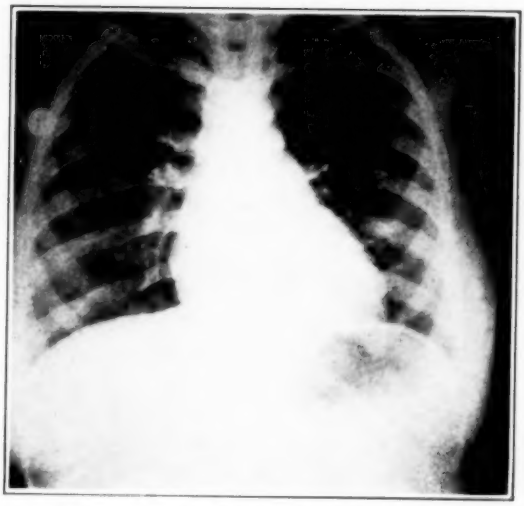

FIG. 2.—Case 1. Roentgen ray of the chest shows no enlarged glands at the lung root.

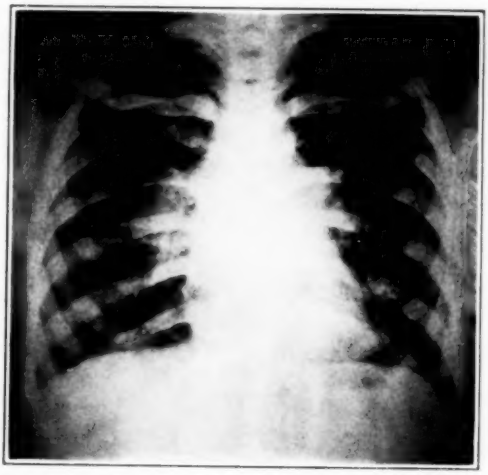

FIG. 3.—Case 1. Two days after admission Roentgen ray of the chest discloses a marked enlargement of the glands at both lung roots. The glands are fairly sharply circumscribed.

FIG. 4.—Case 1.—Film taken 25 days later reveals that the glands are somewhat larger. No other change is noted.

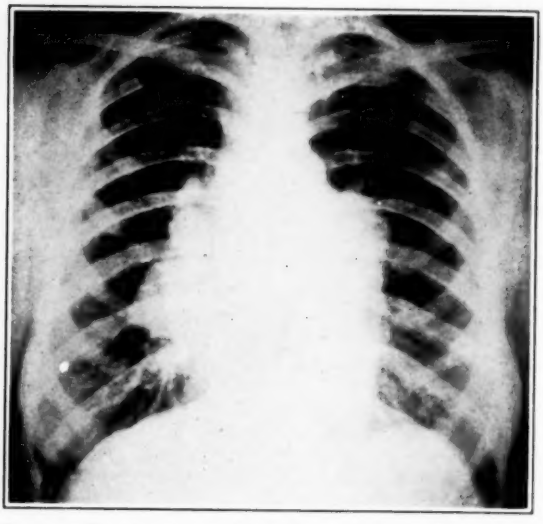

FIG. 5.—Case 2. Roentgen ray of the chest is essentially negative except for bilateral enlargement of the glands at the lung roots. Note the discreteness of these glands. Another film taken one month later, showed no appreciable change, despite adequate radiotherapy.

On discharge, she merely complained of a slight numbness of the face, but the facial weakness was much less apparent. Despite the recession in most of the clinical findings the Roentgen rays of the chest showed progressive changes in the lungs and mediastinum.

Case 2.—A. S., a white married female aged 34, was admitted to this hospital on July 25, 1937, with the complaints of progressive weakness, night sweats, loss of 30 pounds of weight, excessive thirst and frequency of urination, of 6 months' duration. She had been having a low-grade fever running up to 102° F. in the evenings, for 6 weeks prior to her admission. A swelling at the angles of both jaws had been present for about the same period of time. Amenorrhea of 3 months' duration and persistent blurred vision during the same interval were elicited in the history. She had one child and no other pregnancies. The family history, as far as any related condition was concerned, was essentially negative, and irrelevant. Her past history was also negative.

Medical examination revealed a chronically ill female of about 34, well developed and fairly well nourished. A diffuse purulent postnasal drip was seen. The tonsils were markedly enlarged and cryptic. The trachea was in the midline and freely movable. There was a slight increase of retromanubrial dullness to the right and left. A low pitched systolic murmur was heard at the aortic and apical regions, somewhat louder at the former area. On percussion, liver dullness extended to about 3 fingers below the costal margin. The spleen was barely palpable. Several small lymphatic glands were felt in the inguinal regions. Both parotid glands were slightly enlarged but not tender to pressure. Old pigmented areas were noted over both tibiæ, as well as telangiectasiæ over the upper part of the chest wall anteriorly. Blood pressure was 120/70.

Neurologic examination revealed that her visual acuity was markedly reduced. The pupils were both irregular and reacted sluggishly to light and in accommodation. Bilateral uveitis, posterior synechiæ, ciliary injection, deposits on Descemet's membrane and increased relucency of the anterior chamber were noted. Because of the opacities, the fundi oculi were not visualized. There were no extraocular muscle palsies. All the other cranial nerves, grossly tested, were intact. The biceps, triceps and the knee jerks were markedly hyperactive and equally so on both sides. The ankle jerks were present and somewhat diminished. There was no muscle or nerve tenderness. An equivocal Babinski was elicited on the right. Sensation was normal to all modalities.

Laboratory Findings. Urine: Specific gravity 1010 to 1012 with a faint trace of albumin, occasional white cells and coarse granular casts. Blood: Wassermann test, negative. Chemistry in mg. per 100 cc. of blood: Sugar, 95; urea nitrogen, 16; uric acid, 1.6; creatinine, 1; cholesterol, 580; ester, 415; total protein, 6.8%; albumin, 2.2%; globulin, 4.6%; hemoglobin, 84%; white blood cells, 6400; segmented polys, 41; non-segmented polys, 40; lymphocytes, 10; monocytes, 7; eosinophil, 1; basophil, 1.

Electrocardiographic tracings showed a sinus tachycardia, tendency to left ventricular preponderance, and low *T* waves suggestive of involvement of the ventricular musculature. Roentgen ray films of the knees, lumbosacral spine and both shoulders showed no abnormalities of the bones. Roentgenographic film of the chest on June 26, 1937 (Fig. 5), showed a group of moderately enlarged masses at both lung roots. The appearance was that of enlarged glands bilaterally. On July 22, 1937, another plate disclosed no appreciable diminution in the size of the enlarged glands in both lung roots and the findings were practically the same as on the first examination.

Course. The patient received a series of deep Roentgen ray treatments to the mediastinum and to the parotid gland regions. The glandular

enlargement promptly receded during the treatment but the mediastinal glands were not altered. She had fever daily, ranging about 101° F., never reaching the normal level. When biopsy of the parotid glands was suggested the patient signed herself out of the hospital, against advice. She was admitted to the Mount Sinai Hospital on Sept. 23, 1937, and they reported that a biopsy of the tonsils showed fragments of hyperplastic tissue and one epithelioid cell tubercle. Because of an increasing tension in the left eyeball, an iridectomy was performed. The specimen removed was reported as showing fragments of iris with several epithelioid cell tubercles. The patient ran a completely afebrile course during her 6-week stay and there was no change in either the visual disturbances or the evidence of mediastinal lymphadenopathy. At Mount Sinai Hospital the differential diagnosis lay between uveo-parotid tuberculosis and Boeck's sarcoid.

Etiology. Many different etiologic factors have been proposed as the cause of this condition, but the majority of clinicians and pathologists are now of the opinion that tuberculosis is the primary factor. Briefly and for purposes of clarity we have divided the opinions into two groups:

I. *Those Favoring Tuberculosis as a Primary Etiologic Factor.* Lehmann[14] stated that the condition might be due to an atypical form of tuberculosis. Souter[27] expressed the belief that tuberculosis is the cause and stated, "The mechanism that may be assumed is that absorption from tuberculous bronchial or even mesenteric glands causes the parotitis and uveitis and that in the worst varieties of iridocyclitis actual bacilli possibly of a non-virulent type, as suggested by Wilmer, may reach the eye." Search for the tubercle bacillus was unsuccessful until Souter[27] and Tanner and McCurry[29] found it in the lesions. McCurry actually demonstrated the tubercle bacilli in biopsy sections from both parotid glands of a patient suffering from this malady.

Garland and Thomson[9] declared that "In no case in which a biopsy was performed was histologic evidence of tuberculosis lacking," and that they had found incontrovertible evidence of tuberculous infection in more than one-third of 21 recorded cases. Cavara[4] injected material (obtained from biopsies on the lachrymal and parotid glands) intraperitoneally into 3 guinea pigs, with negative results in 2, but produced fatal generalized tuberculosis in 1 which, on autopsy, showed considerable caseation at the site of the injection and in the regional lymph nodes. He concluded that uveo-parotid fever is due to a special type of tuberculosis. Muller[22] reported the case of a boy from whom a biopsy of the parotid gland showed an endothelioid type of tuberculosis, and who presented nodules in the iris morphologically resembling those seen in tuberculosis. McCulloch,[17] on slit lamp examination, noted tubercles along the periphery of both irides in a case reported by him. At times, collateral evidence of tuberculosis is indicated by the family history, clinical signs such as night sweats, lassitude and loss of weight, pleural effusion, cervical adenitis, favorable reaction to tuberculin and roentgenograms.

II. *Those Opposed to the Concept of a Tuberculous Origin.* Authors whose particular cases revealed no clinical features indicative of tuberculosis are mainly in this group. Heerfordt[11] and Leeksma[13] believed that uveo-parotid fever was an atypical form of mumps. Fuchs[7] and others[3,10] were of the opinion that this condition was very closely allied to Mikulicz' syndrome. It was classed as a deficiency disease by Ramsay.[24] Mohr[21] ascribed the lesions to syphilis, because of positive serologic evidence in his case. Infections of the mouth[1,18] and generalized toxemia[6] were also considered as possible causes. Merrill and Oaks[19] attributed this disease to a "specific virus or bacterium as yet undetermined." Because animal inoculation gave negative results, Weve[30] believed that this malady is not truly of tuberculous origin and that it might be a tissue response to an unknown infectious agent allied to tuberculosis and designated it as "paratuberculosis." Parker[23] stated that the "weight of evidence both from the clinical course and the reported cases suggests very strongly that the condition is rheumatic in nature and thus its protean manifestations." That the disease is "an infective allergic condition caused by an organism as yet not isolated, which produces a low grade infection in a sensitized individual" was indicated by Cohen and Rabinowitz,[5] while others[16] are of the opinion that the disease is an allergic reaction to many allergens, one of which may be tuberculosis.

Many competent investigators are opposed to the theory of tuberculosis as the cause of the condition because the results of animal inoculations and tuberculin tests are more often negative than positive, and because, from a clinical point of view, these patients seldom show objective symptoms and signs of tuberculous infection.

Symptomatology. While there seems to be great variation in the order of appearance, severity and duration of the symptoms, they may be considered under:

1. *Prodromata* are frequently, though not constantly, elicited in the anamneses, and may be present from a few days to several months. They include general malaise, weakness, lassitude, drowsiness, anorexia, gastro-intestinal upsets, loss of weight, puffiness of the eyelids, long continued dryness of the mouth, dysphagia, cough, night sweats, pains in the chest, abdomen or joint paresthesias, polyuria without glycosuria and paralysis of other cranial nerves besides the facial. A chronic, low grade fever is common but is not a constant finding. The temperature may range from the slightest elevation to 103° F., in some instances. An afternoon rise is common.

2. *Glandular* enlargement of the parotid glands is a constant finding. It is generally bilateral, but occasionally is unilateral. The glands may be hard or nodular, not adherent to the skin, and while painless, as a rule, may be tender to pressure especially at the onset of the disease. The swelling may be limited to the preauricular

area or be more extensive and involve all of the parotid gland. The enlargement is usually of several weeks' duration but may last for months and even years. The swellings may recur but are usually of a chronic type and resolve without suppuration. In addition to the parotid enlargement, submaxillary, sublingual and lachrymal swelling may occur in the same individual at the same time. Among the lymphadenopathies, cervical gland enlargement is most and bronchial gland is least commonly involved. Hilar gland involvement was also reported.[15,29]

3. *Ocular manifestations* though quite variable are present in all cases and are probably the most important of the diagnostic symptoms in this syndrome. The ocular disturbances may come on suddenly or insidiously and may persist for a week or for years. As a rule, the glandular swellings are the first signs, but in some cases, ocular difficulties, both subjective and objective, either precede or are concomitant with the glandular enlargement. The most prominent eye findings are uveitis with predominance of iritis and cyclitis. It is often the earliest symptom and the resulting visual impairment may be permanent. The onset may be unilateral with pain and dimness of vision or, as invariably occurs, the uveitis may be bilateral and of a nodular type. Other ophthalmologic conditions such as corneal herpes, vitreous hemorrhages and opacities, keratitis, optic neuritis or atrophy, neuroretinitis, choreoretinitis, aqueous turbidities, conjunctivitis, glaucoma and cataract may occur. They may also include mistiness or dimness of vision with more or less impairment of sight, narrowing of the palpebral fissures and ciliary congestion. The pupils may be dilated, irregular and fixed to light and in accommodation. There may be posterior synechiæ or one may note fatty deposits in the posterior surface of the cornea and the anterior surface of the lens. Nodules, definitely identified as tuberculous, are said to occur in the iris of these patients.

4. *Neurologic complications* have received comparatively little attention as they are overshadowed by the parotid and ocular manifestations. Levin[15] expressed the opinion that 50% of the cases present some abnormality of the nervous system. Neural involvement shows great variability and may range from cranial to peripheral nerve affections.

Facial palsy, usually of the peripheral type and of varying degrees of intensity and duration, is the commonest neurologic complication. It may be bilateral although it more frequently is unilateral. Whether the palsy results from pressure on the nerve by the swollen gland is still a moot and unsettled question. As a rule, the facial nerve involvement, when it occurs, follows the parotitis in from a few days to 6 months, but in several instances it has preceded the parotitis by varying lengths of time and in other cases the facial impairment occurred simultaneously with the parotitis. Because

the paralysis is often limited to the lower part of the face, Garland and Thomson[9] explained the peripheral facial palsy on the basis of pressure by the parotid gland on the nerve as it leaves the stylomastoid foramen, whereas there was evidence (involvement of taste in the anterior two-thirds of the tongue) in Mohn's[20] case to place the site of the lesion somewhere between the geniculate ganglion and the branching of the chorda tympani (in the bone itself) thus excluding pressure from the parotid gland, which, incidentally, was not yet enlarged. Facial palsy developing when the parotitis is subsiding is probably due to the cirrhotic nature of the inflammatory lesion.[9] Altland-Duisburg[2] thought that the facial paralysis is due to a toxin analogous to that producing the paralysis in the late stages of diphtheria and that it indicated rather a particular causative agent. Tait[28] believed that the neuritic manifestations may be due to a circulating toxin.

Among the other cranial nerve impairments, diplopia and strabismus are rare. Partial ptosis of the eyelids, unilateral or bilateral, is not uncommon. In both of our cases ptosis was a prominent presenting sign. Pupillary changes secondary to the uveitis are fairly common. Involvement of the sensory portion of the trigeminal nerve was mentioned,[15] but the motor portion, as far as we could find, was not involved in any of the cases thus far reported. Nerve deafness of the central type is occasionally encountered.[9,20,27] Dysphagia is fairly common and has been considered to be evidence of cranial nerve paralysis by many investigators, but others[9] thought it was due to the lack of salivary secretion resulting from the parotitis. Vocal cord paralysis[11,28] and paralysis of the soft palate[24] are rarer findings. Dysarthria is occasionally a prominent symptom[27] and has been attributed both to dryness of the mouth and to muscular weakness following the facial palsy. Loss of the sense of taste, disturbance of the innervation of the uvula and hypesthesia of one side of the tongue[5] are very rare. Hallucinations and meningeal signs have been noted. Delirium and convulsive seizures occurred in 1 case, and at autopsy, multiple tuberculomas were found.[3] Hypersomnia is not uncommon.

Involvement of the spinal nerves may be manifested by a diminished tactile, pain and temperature sense, reduction or abolition of the deep tendon reflexes, tenderness over the peripheral nerves, paresthesias, and wrist or foot drop. The knee jerks may be markedly diminished or absent,[9] the ankle jerks may not be elicited, or all the deep tendon reflexes may be depressed or abolished.[9,20,27] Intermittent claudication, paralysis of the extremities, with definite pyramidal tract involvement have been reported.[3]

5. *Other Manifestations.* A. *Polydypsia and polyuria* associated with a dilute but otherwise essentially normal urine have been noted. Levin[15] believed that these symptoms represented a true diabetes insipidus.

B. *Skin lesions:* early in the illness, there is not infrequently a patchy, non-elevated erythematous rash, without itching and involving particularly the extensor surfaces of the arms and legs. The rash is generally of short duration. Other skin eruptions include erythema nodosum,[19,24] xerodermia of both legs,[8] papulonecrotic tuberculosis,[25] urticaria, and petechiæ.[12]

C. *Joint pains and polyarthritis* have also been reported.[19,27]

D. *Amenorrhea* is not an infrequent finding,[8,26] and was present in Case 2.

Laboratory Findings. 1. *Urine* is generally negative, except for a low specific gravity when there is an altered water metabolism.

2. *Blood*, as a rule, reveals no definite abnormalities except for an occasional secondary anemia. In some instances, eosinophilia has been noted.

3. *Spinal fluid* may reveal a moderate pleocytosis (5 to 20 lymphocytes) or a slight increase in protein content or both.

4. *Wassermann tests* are generally negative both in the blood and spinal fluid.

5. *Tuberculin test* is more often negative than positive.

6. *Electrocardiograms* in some cases are abnormal, suggestive of myocardial involvement.

7. *Roentgen rays* of the chest, in many cases, sooner or later disclose varying extents of pulmonary lesions, especially enlargement of the glands at the lung roots. Roentgen rays of the skull and long bones have not revealed any gross defect.

Differential Diagnosis. 1. *From Mumps.* The fact that many of the patients had mumps in childhood, and that at the time they had uveo-parotid fever, they had not been exposed to mumps, the long prodromal period, the chronic nature of the condition, the frequent bilateral facial palsy, which may antedate the parotitis, the absence of orchitis, and further, that individuals in contact with these patients did not develop a similar condition, should conclusively eliminate mumps in the differential diagnosis.

2. *From Syphilitic Parotitis.* In early syphilis the gland swells rapidly, is tender to touch and has a firm, tense, reddish surface. The swelling is usually bilateral but not symmetrical. Suppuration may occur in the neighboring lymph nodes. The mass is closely adherent to the underlying tissues. In late syphilis the parotitis develops insidiously. The tumor mass becomes attached to the underlying tissues and the skin. Fluctuation develops with the eventual appearance of a gummatous ulcer. Syphilis can be easily ruled out by history, examination and serologic findings.

3. *From Mikulicz' Disease.* This is a rare and still obscure malady, characterized by a chronic swelling of the salivary glands, particularly the parotids, but also involving the submaxillary and sublingual glands and occasionally the lachrymal glands. The patients frequently develop tuberculosis later. Here, ocular mani-

festations seldom occur. Mikulicz' disease in many ways seems to be allied to uveo-parotid fever, and, at times, a group of cases of one disease probably contains instances of the other.

4. *From Boeck's Sarcoid.* This condition should be considered where lesions suggestive of tuberculosis are found but no caseation or tubercle bacilli can be demonstrated. However, Boeck's sarcoid differs somewhat from uveo-parotid fever in several ways. In the former disease, there are characteristic skin manifestations which may assume one of three forms, *i. e.*, small disseminated nodules, infiltrations or large cutaneous nodosities. Roentgen rays of the hands and feet show a reticulum-like appearance in the small bones which may extend to the long bones. Pathologically, the lesions in both conditions may manifest the same features (a miliary epithelioid tubercle with occasional giant cells, but with almost complete absence of necrosis). Many authors are of the opinion that the two diseases are one and the same.

5. *From Encephalitis Lethargica.* That uveo-parotitis may simulate encephalitis has been commented upon by Levin. However, in obscure cases of encephalomyelitis or polyneuritis, especially when complicated by parotitis, the diagnosis of uveo-parotid fever must be borne in mind.

Prognosis and Treatment. The prognosis is good, and the mortality is estimated at about 5%. Death, in the rare instances in which it occurs, is due to miliary tuberculosis. The disease runs a chronic course, and one of its features seems to be the irregularity in the onset and progression of the symptoms. Regardless of the duration of the parotitis, its tendency is to improvement without suppuration, but it may recur. The ocular symptoms, however, may persist or even become permanent.

Some authors have advocated symptomatic treatment with tonics, such as inorganic arsenic, whereas others have employed thyroid extract, foreign protein, tuberculin and Roentgen ray therapy.

Summary and Conclusions. Our study indicates the comparative rarity of uveo-parotid fever even in a large general hospital. The condition is probably more common than is usually suspected, but is rare enough not to be readily discerned. To date, less than 100 cases have been reported and the majority have appeared in Scandinavian and German journals of ophthalmology. A review of the literature reveals a multiplicity of suggested etiologic factors among which are atypical mumps, syphilis, beri-beri, diphtheria, allergic reaction, toxemia, oral sepsis, virus, infection and pseudoleukemia. It has also been designated as a variety of Mikulicz' disease. Most of these theories have been abandoned and the problem now resolves itself into whether this clinical entity is due to tuberculosis or to some as yet undiscovered infectious agent such as a virus. There is considerable, though not altogether conclusive, evidence in support of the tuberculous theory. However, none of the theories

so far advanced has an unassailable foundation. Our knowledge of uveo-parotid fever will be materially aided if and when either the causative agent of Boeck's sarcoid is found or when there are many more unequivocal demonstrations of tubercle bacilli in the lesions. Until then, the assumption of a tuberculous basis seems plausible and probable, but that it may be a specific infection due to an unknown virus cannot with absolute certainty be excluded.

The symptoms are essentially a uveitis associated with a parotitis, with a low grade chronic fever. There are many prodromata. Neurologic complications are common. The disease is to be differentiated from mumps, syphilitic parotitis, Mikulicz' disease, Boeck's sarcoid and encephalitis lethargica. The prognosis is good as to life and fair as to residua.

We are indebted to the medical department for its coöperation and permission to publish these cases.

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REGENERATION OF THE ADRENAL GLAND FOLLOWING ENUCLEATION.

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We have shown previously that when the adrenal glands are removed from their normal position and grafted elsewhere in the same animal, complete degeneration of the medulla and entire

cortex takes place, except for a narrow zone of glomerulosa and capsule. From these persistent tissues, however, a functional mass of cortical tissue rapidly regenerates, and in a few weeks a gland, without medulla, equal to or greater in size than the original gland, is restored. Likewise, we have shown that when the capsules, with a narrow zone of cortical cells adherent to them, are removed from the rest of the gland and grafted to the ovaries, a functional mass of cortical tissue will soon regenerate. However, when the central portions of the gland, including medulla and most of cortex but without the capsule, are grafted, then regeneration does not take place.

Enucleation is a method employed by physiologists to free the adrenal gland of all medullary tissue and yet secure an adequate amount of cortex to meet the functional requirements of the organism. Evans[2] in studies on the adrenal cortex and carbohydrate formation described this method of securing demedullated adrenal glands. Scant attention, however, has been paid to factors which control the extent of regeneration of cortical tissue after the medulla and most of the cortex of the gland have been removed.

This report is concerned with the regeneration of the enucleated adrenal gland as influenced by: 1, the presence or absence of one intact adrenal gland; 2, treatment with cortin; 3, removal of the pituitary body; and 4, age.

Methods. Rats of the Wistar strain were used in these experiments. Unless otherwise designated, male animals weighing 170 to 200 gm. were selected. Enucleation was carried out through a lumbar incision. The adrenal gland was located and carefully freed of its fat investment. Without damage to the blood supply the anterior tip of the gland was carefully excised and then, with fine forceps, the body of the gland, including all of the medulla and most of the cortex, was gently expressed. The remaining capsule and the narrow zone of glomerulosa adhering to it was then replaced and the peritoneum closed. Data collected on the weights of adrenal glands and on the amount of glandular material expressed from the capsule indicated that there was left after enucleation of the adrenal gland an amount of adrenal substance, including capsule, weighing approximately 3 mg.

Hypophysectomy was carried out employing the usual parapharyngeal approach. The glands were removed by negative pressure. When partial hypophysectomy was performed, the anterior lobe was divided into two halves by means of a fine needle. The one-half of the anterior lobe was removed with a fine pipet, exposing the posterior lobe which was similarly removed, thus leaving one-half of the anterior lobe intact.

Bilateral enucleation was always performed as a single stage operation. When unilateral enucleation was carried out, the left adrenal gland was always enucleated and the right adrenal gland was either left intact or removed completely from the body. In those animals which were hypophysectomized, bilateral enucleation of the adrenal glands was carried out at the same time. It was necessary to treat the hypophysectomized adrenal-enucleated animals with 1 cc. of cortin, which was given daily by subcutaneous injection. This amount is inadequate to inhibit regeneration of the adrenal glands of non-hypophysectomized rats.

The rats were maintained on a commercial diet containing 0.24% sodium and 1% potassium. The animals were killed by exsanguination. The

regenerating cortical masses were weighed by a standardized procedure and were to the nearest milligram. All adrenal tissue was fixed and stained with hematoxylin and eosin, and for the chromaffin reaction.

Procedures. Four individual experiments were carried out. In Experiment 1, 28 rats were closely matched on a basis of weight into 14 pairs. The left adrenal gland of each animal was enucleated. In 6 animals the right adrenal gland was removed from the body at the time of enucleation, and in the other animal of the pair the right adrenal gland was left intact. One pair of these animals was killed each week. In the case of the 8 remaining pairs of animals the right adrenal gland was removed from 1 animal of each pair 2 months after enucleation of the left adrenal. In the other animal of the pair the right adrenal gland was left intact. One pair of these animals was then killed at weekly intervals for 8 weeks.

In Experiment 2, the left adrenal gland was enucleated in 38 animals. All of these animals were closely matched on a basis of weight, and each animal was designated to an experimental group by chance selection. In a group of 12 of these 38 animals the right adrenal gland was removed. In a second group of 10 animals the right adrenal gland was left intact. In a third group of 6 animals the right adrenal gland was removed and the animals were given 2 cc. of cortin subcutaneously every 8 hours. In a fourth group of 10 animals the right adrenal gland was removed and the animals were given 5 cc. of cortin daily in their drinking water. All animals were killed for necropsy 21 days after operation.

In Experiment 3, bilateral enucleation of the adrenal glands was carried out in 70 adult female rats. In 30 animals of this group complete hypophysectomy was performed; in 10 additional animals the posterior lobe and half the anterior lobe of the pituitary were removed. The remaining 30 animals were not hypophysectomized. One hypophysectomized and 1 non-hypophysectomized rat were killed daily for 28 days after operation. All of the partially hypophysectomized, adrenal-enucleated animals were killed 30 days after operation. In this experiment the glands were not weighed at necropsy.

In Experiment 4, we compared the effect of the presence or absence of the right adrenal gland on the extent of regeneration in the enucleated (left) gland of 6 pairs of newborn female rats and of 8 pairs of female rats which were more than 2 years of age. In this experiment the glands were not weighed at necropsy.

Results. The results of Experiment 1 are summarized in Fig. 1 and in Table 1. When the right adrenal gland was removed regeneration proceeded rapidly from the remaining capsule of the left adrenal gland. At 5 to 6 weeks after enucleation cortical masses weighing 14 to 16 mg. had regenerated from the remnant which had remained (Figs. 1*a* and 3). When the right adrenal gland was left in place, regeneration of cortical tissue in the enucleated gland did not occur to an appreciable extent. Since approximately 3 mg. of tissue had been left at operation, and since the weights obtained (Fig. 1*b*) did not exceed that figure, it seemed clear that no significant amount of regeneration occurred during the period of 4 months. Stained sections of these adrenal capsules removed 4 months after enucleation showed some few, very small discrete masses of cortical tissue. When the right adrenal gland was left intact for a period of 2 months and was then removed from the animal, immediately the capsule which had been relatively inactive for 8 weeks was

stimulated to cortical proliferation, so that in 1 week a cortical mass weighing 5 mg. was recovered. After 7 and 8 weeks the adrenal cortical masses weighed 23 and 17 mg., respectively (Fig. 1*c*).

TABLE 1.—WEIGHTS (MG.) OF REGENERATED ENUCLEATED ADRENAL GLANDS AS INFLUENCED BY THE PRESENCE OR ABSENCE OF THE OPPOSITE GLAND.

Time (weeks).	Right adrenal removed at time of enucleation.	Right adrenal present.	Right adrenal removed 2 months after enucleation.
1	4	3	
2	7	3	
3	10	2	
4	10	2	
5	16	3	
6	16	2	
7			
8			
9		2	5
10		2	7
11		3	17
12		2	11
13		2	18
14		3	14
15		3	23
16		1	17

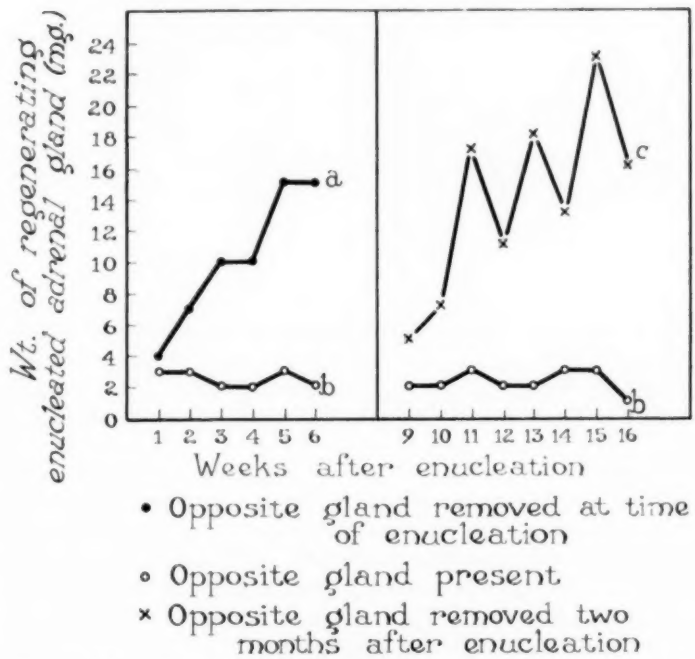

FIG. 1.—Weights of regenerated enucleated adrenal glands at various intervals following enucleation.

The results of Experiment 2 are summarized in Figure 2 and in Table 2. It was again demonstrated that the presence of one

TABLE 2.—WEIGHTS OF REGENERATED ENUCLEATED LEFT ADRENAL GLAND.

Group.	No. of animals.	Weight of gland (mg.) after 3 weeks.	Average weight.
I. Right gland removed	12	7, 8, 9, 10, 10, 11, 12, 13, 13, 13, 13, 14	11.1
II. Right gland intact	10	1, 1, 1, 1, 2, 2, 2, 2, 2, 3	1.7
III. Right gland removed*	6	3, 3, 4, 5, 5, 8	4.7
IV. Right gland removed†	10	1, 1, 1, 1, 1, 1, 1, 1, 1, 3	1.2

* 2 cc. of cortin administered subcutaneously every 8 hours.
† 5 cc. of cortin administered daily to each rat in drinking water.

intact adrenal gland will effectively inhibit regeneration of the enucleated gland, whereas regeneration occurs rapidly when the intact adrenal gland is removed. Experiment demonstrated that 5 cc. of cortin per day added directly to the drinking water was adequate

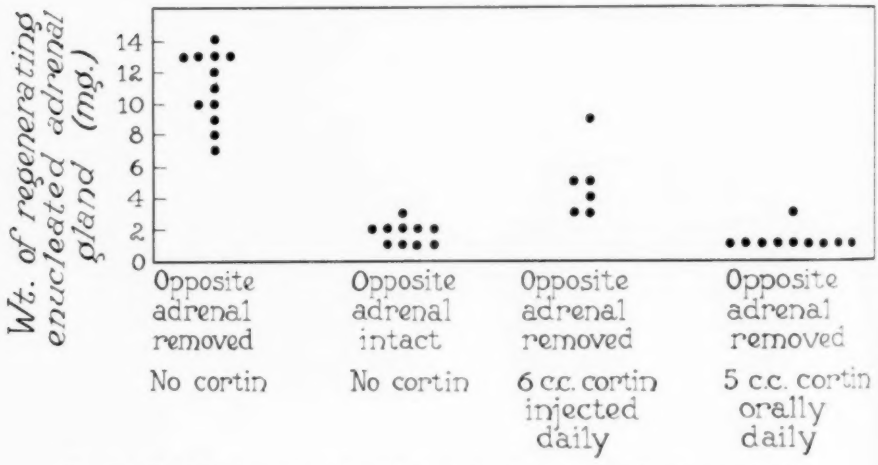

FIG. 2.—Weights of regenerated enucleated adrenal glands 3 weeks after enucleation.

to suppress completely the regeneration of the left adrenal gland even when the right adrenal gland had been removed (Fig. 4). Other data which are not reported here have shown that when smaller amounts of cortin were administered, the enucleated adrenal gland regenerated varying amounts of cortical tissue. When given by subcutaneous injection, cortin was less effective than when given by mouth. The daily administration of 6 cc. of cortin parenterally was inadequate to prevent some degree of regeneration in the enucleated gland (Fig. 2).

No quantitative data are presented for Experiment 3, since the extent of regeneration was an "all or none" response. When both adrenal glands were enucleated at the same time, regeneration of

cortical tissue followed very rapidly in the case of those animals that were not hypophysectomized. In a few weeks, masses of cortical tissue equal in size to, or larger than, the amounts of cortical tissue in the original glands had been restored. When the pituitary glands were completely removed at the same time that both adrenal glands were enucleated, regeneration of cortical tissue did not occur. Histologic comparison of the enucleated glands from the hypophysectomized animals with the enucleated glands of the non-hypophysectomized animals fully confirmed this conclusion. In the hypophysectomized animals there was occasionally observed a viable capsule and small portions of cortex approximately equal in amount to that left at operation. In animals in which half of the anterior lobe remained, regeneration of the enucleated glands occurred to approximately the same extent as in the non-hypophysectomized animals.

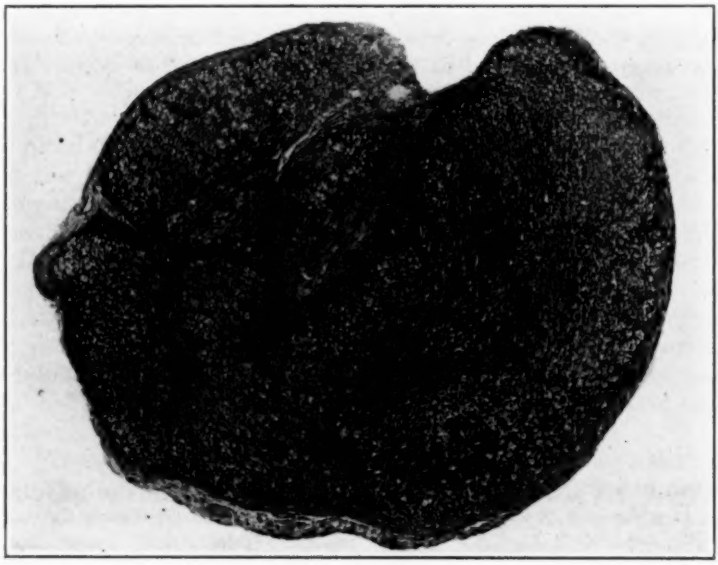

FIG. 3.—Regenerated adrenal gland 5 weeks after enucleation and removal of the opposite gland. (× 30.)

In Experiment 4 it was clearly shown that regeneration of the enucleated adrenal gland will occur in either the young or senile animal when the intact adrenal gland is removed. Regeneration was completely suppressed by the presence of one intact gland in the cases of both young and senile animals. No quantitative data are presented since histologic examination of the tissue showed clearly that regeneration of cortical tissue in this experiment was an "all or none" response.

Comment. It seems clear from these results that the presence of one intact adrenal gland will suppress regeneration of cortical tissue in the other enucleated gland. This observation confirms the earlier observations of Wyman[4] and of ourselves[3] that an autograft of an adrenal gland will not regenerate when the other, or even a part of the other gland is left in place.

These observations further show that the daily administration of cortin was equally effective in suppressing regeneration of the enucleated gland. The cortin used in these experiments was an active, well standardized preparation which had been shown by the Ingle rat test to increase the work performance of adrenalectomized rats when administered in amounts of 0.2 cc. twice daily. It is

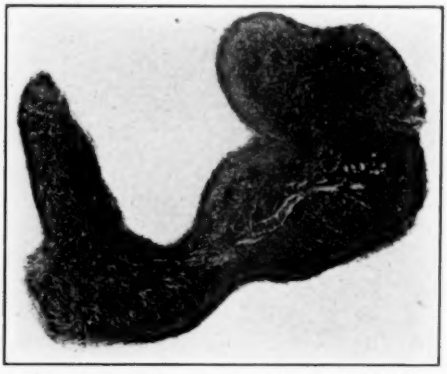

FIG. 4.—The enucleated gland in an animal from which the other intact gland had been removed, 3 weeks after operation; 5 cc. of cortin given daily by mouth. (× 30.)

significant that large amounts of cortin were required to suppress cortical regeneration entirely. Normal amounts of cortex regenerated when minimal maintenance doses of cortin were given. Even amounts which increased work performance following total adrenalectomy failed to inhibit regeneration. Five cubic centimeters of cortin a day administered orally was required to suppress it completely.

Many investigators have been unable to restore all of the functions associated with the adrenal cortex by giving cortin. It is quite probable that insufficient amounts of cortin were given, for a wide difference exists between the minimal amounts of cortin essential for life and the amounts essential for completely normal physiologic activity. Furthermore, in the usual attempts at replacement therapy, intermittent injection is substituted for what is probably a continuous secretion of the normal gland. It is reasonable to assume that large amounts of hormone may be lost by the organism when it receives intermittent injections. In this and other unpublished data we have confirmed the observation of D'Amour and Funk[1] that cortin may be more effectively utilized when given to

the rat in its drinking water than when given parenterally. Likewise we have noted that cortin is more effectively utilized by rats when it is dissolved in oil than when it is dissolved in water.

Our observation that regeneration of the adrenal cortex does not occur in hypophysectomized rats confirms Wyman's report that transplanted adrenal glands will not become established in hypophysectomized rats. We believe that regeneration of adrenal tissue is stimulated by the adrenotropic principle elaborated by the anterior pituitary, and that regeneration will not occur when this hormone is absent. We have not, however, confirmed Wyman's deduction that the extent of regeneration of the adrenal gland is uninfluenced by the administration of cortin.

It may be important that the adrenotropic function of the anterior pituitary was still adequate when the anatomic association of the pituitary to the hypothalamus was broken by removal of the posterior lobe. Whether the anterior pituitary is self-sufficient in its regulatory functions has not been satisfactorily proved. It may be deduced from these observations that its normal anatomic relationship to the hypothalamus (involving possible nervous control) is not essential for it to secrete its adrenotropic principle.

Summary and Conclusions. A study has been made of some of the factors which regulate the regeneration of cortical tissue after the medulla and most of the cortex of the adrenal glands of white male rats had been removed. The following conclusions have been reached:

1. When one adrenal gland is enucleated and the other removed, adequate cortical regeneration proceeds within the enucleated gland.

2. When one adrenal gland is enucleated and the other left intact, there is no, or only very slight, regeneration within the enucleated gland. The presence of one functioning gland suppresses regeneration within the other enucleated gland.

3. If a normal adrenal gland is removed 8 weeks after the other gland had been enucleated, regeneration within the enucleated gland is then stimulated to occur in the normal way.

4. The oral administration of 5 cc. of cortin daily, completely suppresses regeneration within an enucleated gland, even when the other adrenal gland has been removed.

5. The subcutaneous administration of amounts of cortin comparable to those given by mouth will restrict, but not completely suppress, cortical regeneration within the enucleated gland.

6. Hypophysectomy coupled with bilateral enucleation of the adrenal glands completely suppresses regeneration of cortical tissue. In the presence of half of the anterior lobe of the pituitary there is normal regeneration in the enucleated adrenal gland.

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THE EFFECTS OF A PRESSOR SUBSTANCE OBTAINED FROM THE KIDNEYS ON THE RENAL CIRCULATION OF RATS AND DOGS.*

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In 1898, Tigerstedt and Bergman[8] reported that the injection of extracts of kidneys of rabbits caused a moderate and well-sustained elevation in blood pressure. Their observations have subsequently been confirmed by several groups of investigators, including Bingel and Strauss,[2] Bingel and Claus,[1] Hessel and Hartwich,[5] Harrison, Blalock and Mason[3] and Prinzmetal and Friedman.[7] The initial observations by Tigerstedt and Bergman and by Bingel and Strauss indicated that the pressor principle was a large molecular substance of protein nature, being non-dialysable, insoluble in various organic solvents and precipitated by ammonium sulphate in proper concentration. More recently Hessel and Hartwich,[5] studying renal press juice, allowed to autolyze in an incubator, found that after several days a highly active small molecular pressor substance appeared. J. R. Williams, Harrison and Mason[9] found that a non-specific pressor agent developed when organs other than the kidney were allowed to undergo digestion. The non-specific pressor substance was found to have the chemical and pharmacologic properties of tyramine and was believed to be tyramine or some closely related substance. However, the latter authors, in agreement with previous workers, found that "renin" (the name given to the large molecular renal pressor substance by Tigerstedt and Bergman) was present in significant quantities only in the kidney. It therefore appears that under different conditions two different blood pressure raising principles may be obtained from renal tissue, one of them being of protein nature and specific for the kidney; the other probably being an aromatic amine and not specific.

At the present time information is lacking as to whether these two pressor substances are in any way concerned in the regulation of vascular tonus in health or in disease. Since the kidney seems, on the basis of the available evidence, to be the only source of one of them and to be one of the possible sources of the other, one might expect that any vascular action which these agents have would be particularly pronounced on the renal vessels. The object

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of the experiments to be reported was to study this question. A few observations have been made concerning the action of tyramine but most of the work has been concerned with investigation of the effects of "renin" on the renal blood flow, the volume of kidney and the rate of urine formation.

Material. Fresh pig kidneys were obtained from the slaughter house and the cortex separated from the medulla, which was discarded. After the cortex had been put through a meat grinder, 20 gm. aliquots were ground with carborundum to a fine paste. Nine volumes of 95% alcohol were then added gradually, the paste being ground further during this addition. The mixture was then placed in large centrifuge tubes and allowed to stand in the ice box for 1 or more days. Shortly before the renal extract was to be injected the alcohol-kidney mixture was centrifuged, the alcohol discarded and the residue dried by spreading it out in a thin layer on a flat plate. After the kidney residue had been dried into a powdery state it was ground in a mortar with an amount of water equivalent to 2 cc. per gm. of original kidney cortex. This mixture was centrifuged and the supernatant fluid employed for injection. In order to determine whether the effects observed were specific for renal extracts injections were made of similar preparations from liver and from spleen.

Experiments on Rats. Large white rats weighing 300 gm. or more were anesthetized by the intraperitoneal injection of sodium pentobarbital—4 mg. per gm. of body weight. The abdominal aorta was then cannulated, heparin was injected and blood pressure recorded with a small-bore mercury manometer. A calibrated pipette was attached to a metal cannula inserted into the vena cava immediately below the renal veins. The vena cava was then freed just above the point of entrance of these veins so that it could be occluded at will with a bull-dog clamp. Measurements of renal blood flow were made by suddenly clamping the cava and at the same time removing the clamp between the venous cannula and the pipette. The time required for the column of blood to pass between two marks on the pipette was noted. After such a measurement the clamp on the cava was removed allowing the blood in the pipette to return to the circulation and the renal venous return to proceed along the normal channels. Following several measurements renal extract was injected through a side connection of the aortic cannula and its effect on the blood pressure and the blood flow through the kidney noted. The volume of renal extract injected was 0.5 to 1 cc. For purposes of control similar volumes of 0.9% sodium chloride solution were administered alternately with the injections of the renal extract.

Results With Rats. Satisfactory preparations were obtained with 3 rats, 7 injections of "renin" and of saline, respectively, being made. Significant rise—*i. e.*, of more than 10 mm. of mercury—in blood pressure occurred twice following the injection of salt solution, the increase being evanescent. Significant increase in blood pressure occurred 5 times following injection of "renin," the rise being well sustained in each instance. The initial administration of "renin" was followed in each rat by a well-marked and sustained increase in blood pressure, subsequent injections producing less effect. In each instance the increase in blood pressure produced by renal extract was preceded by a marked but transient decline lasting only a few seconds. (The substance or substances respon-

sible for this initial decline in blood pressure is not "renin" for this depressor effect occurs following the administration of similarly prepared extracts of organs other than kidney. Since the method of preparation makes the presence of histamine and other small molecular pressor substances unlikely, it seems probable that the initial depressor effect is due to peptones, but of this point we are not certain.)

The administration of salt solution caused in each of 7 instances a slight increase in the renal blood flow. The injection of "renin" was, on the other hand, followed in each of the 7 observations by a pronounced and sustained diminution in the renal blood flow. This diminution was maximal at a time when the blood pressure was above the level before the injection. It persisted after the

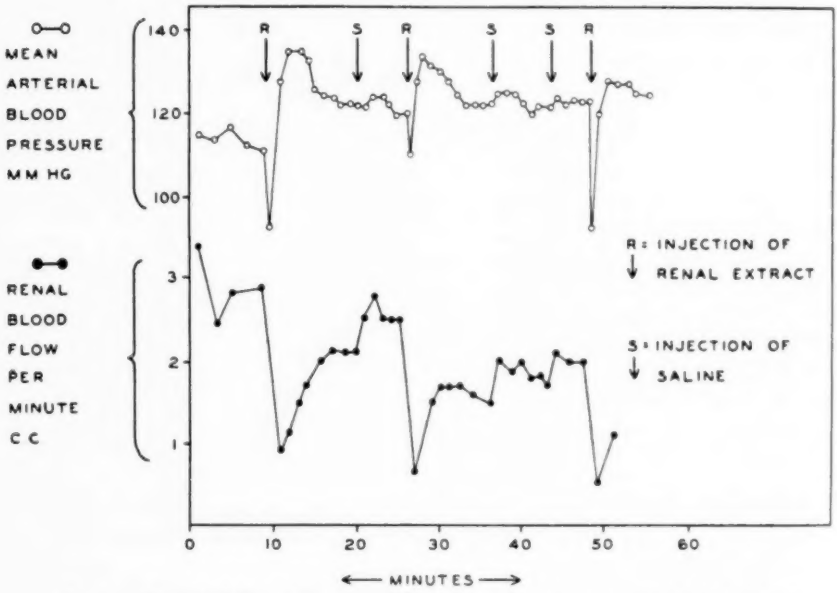

FIG. 1.—The administration of renal extract ("renin") to rats caused rise in blood pressure and decline in renal blood flow, the latter effect being more prolonged. (The initial decline in blood pressure was apparently due to impurities as it occurred when extracts of other organs were injected.)

blood pressure had returned to the previous level, and occurred even when the pressor response to renal extract was minimal. The changes in blood pressure and in the renal blood flow are illustrated in Fig. 1.

These experiments suggest that the large molecular pressor substance (Tigerstedt's "renin") has a pronounced action on the blood-vessels in the kidney. In order to localize more definitely its site of action, attempts were made to measure the urine flow

and the kidney volume of rats. Such attempts were not successful and accordingly further experiments were undertaken on larger animals.

Experiments on Anesthetized Dogs. Dogs weighing 12 to 16 kg. were anesthetized by the intravenous injection of sodium pentabarbital, 30 mg. per kg. of body weight. The renal blood flow was measured by passing a specially constructed cannula into the inferior vena cava through the external jugular vein, according to the technique devised for the coronary blood flow by Harrison *et al.*[4] and modified for measurement of the blood flow through the kidneys by Mason *et al.*[6] Heparin was used as an anticoagulant. The blood pressure in the femoral artery was recorded with a mercury manometer. In some of the experiments a plethysmograph was inserted on one of the kidneys through a flank incision, and in a few instances urine was collected from a catheter in the bladder. After several preliminary measurements of the blood flow through the kidneys renal extract was injected and its effect on the several functions noted. The amount of the extract injected varied in these experiments from 10 to 40 cc., corresponding respectively to from 5 to 20 gm. of renal cortex. In order to determine the effects of the injection of equivalent volumes of fluid and to learn whether the effects observed were dependent on substances present only in the kidney, 3 experiments were done in which extracts of liver tissue prepared in a similar way to the kidney extracts were administered. A number of observations were also made concerning the action of tyramine monohydrochloride (Pfansthiel), which was administered in doses of 0.5 to 1 mg. per kg. of body weight.

Results With Dogs. (See Table 1 and Fig. 2.) Except for an evanescent decline in blood pressure consistent effects were not observed from the administration of the extract of liver. Kidney extract, on the other hand, usually caused increase in blood pressure, diminution in renal blood flow, some swelling of the kidney, and an

TABLE 1.—THE EFFECTS OF RENAL EXTRACT ("RENIN"), OF LIVER EXTRACT AND OF TYRAMINE ON THE RENAL CIRCULATION OF DOGS ANESTHETIZED WITH SODIUM PENTABARBITAL.

Function studied.	Source of extract.	Number of observations.	Increase.	Decrease.	No change.*
Mean arterial blood pressure	Kidney	13	9	2	2
	Liver	3	0	2	1
	Tyramine	13	13	0	0
Renal blood flow	Kidney	11	1	9	1
	Liver	3	0	1	2
	Tyramine	13	0	11	2
Volume of kidney	Kidney	9	7	1	1
	Liver	3	0	1	2
	Tyramine	10	1	8	1
Rate of urine secretion	Kidney	3	3	0	0
	Liver	3	1	1	1
	Tyramine	2	0	1	1

* Changes of less than 10% in the rate of blood flow and of urine formation and of less than 10 mm. of mercury in arterial blood pressure were not considered significant. In compiling the table, evanescent diminution in blood pressure occurring immediately after the injection of tissue extracts and disappearing in 1 or 2 minutes have been neglected.

increase in the amount of urine formed. These changes were not encountered in every experiment, which is not surprising in view of the impure character of the extracts. Tyramine caused well-marked elevation of blood pressure, diminution in the renal blood flow, and shrinkage of the kidney.

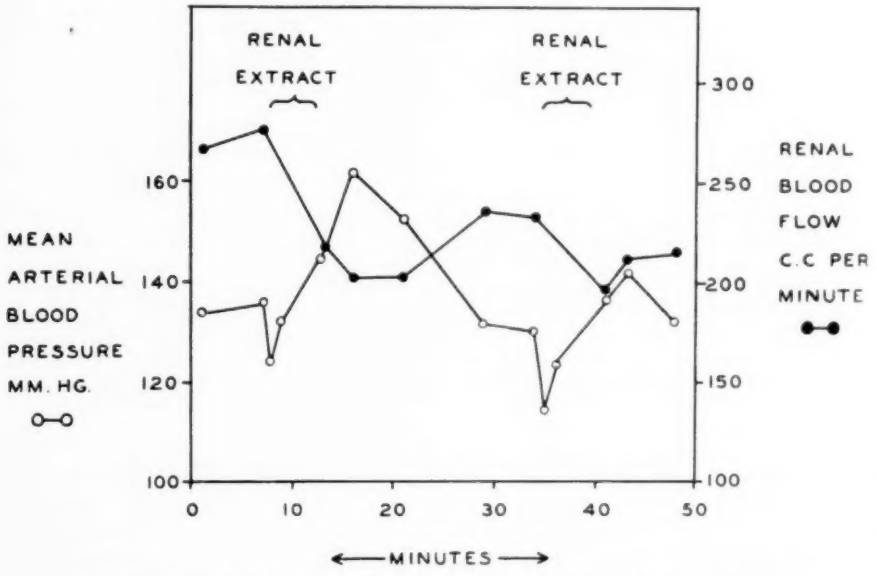

FIG. 2.—The administration of renal extract ("renin") to dogs caused rise in blood pressure and decline in renal blood flow the latter effect being more prolonged (The initial decline in blood pressure was apparently due to impurities as it occurred when extracts of other organs were injected.)

Observations on the Rate of Urine Formation in Unanesthetized Dogs. It was not possible to measure renal volume and renal blood flow in unanesthetized animals, but it was thought that some indication could be obtained of the functional changes in the kidney of normal animals by measurements of the amount of urine formed after the administration of renal extract or of tyramine. Accordingly a series of such experiments were undertaken, urine being collected by a catheter in the bladder, and the volume excreted during each 5-minute period noted. In some of the experiments, 400 cc. of water were given the animals by stomach tube at the start of the experiment, while in other instances no fluid was given. After the urine volume had been relatively constant during several successive 5-minute periods, intravenous injections of renal extract, liver extract, splenic extract or of tyramine were made. Only 1 injection was made into a given dog on the same date but the same group of animals was used throughout the study. The results of

these observations are summarized in Table 2. Constant effects were not obtained from the extracts prepared from the liver or spleen. On the other hand, in most of the experiments the kidney extracts resulted in a slight to well-marked diuresis, while tyramine caused diminution or no change in the amount of urine secreted.

TABLE 2.—THE EFFECTS OF RENAL EXTRACT ("RENIN") AND OF TYRAMINE ON THE RATE OF URINE FORMATION OF UNANESTHETIZED DOGS.

Source of material injected.	Number of experiments.	Effect on urine flow.			Remarks
		Increase.	Decrease.	No change.	
Kidney	8	6	1	1	No additional fluid given.
Kidney	8	6	1	1	400 cc. of water given by stomach tube before experiment.
Spleen	7	2	2	3	
Tyramine	5	0	3	2	

Comment. Since tyramine caused diminution in renal blood flow and shrinkage of the kidney in spite of a well-marked increase in the blood pressure, it seems likely that this substance causes contraction of the afferent glomerular arterioles or possibly of the small arteries in the kidney.

The interpretation of the results observed after the injection of "renin" is less certain. It seems clear that the renal extract had effects which were different from those of the similarly prepared extracts of liver and spleen. However, one cannot be sure that the alterations in the different functions studied were all due to the substance which caused elevation of blood pressure, because the extracts were not sufficiently purified. With this limitation in mind the findings are interpreted as indicating that since the renal extract produced swelling of the kidney, diuresis, and diminution in renal blood flow in spite of elevated blood pressure, it probably caused contraction either of the efferent glomerular vessels or of the smaller renal veins. Whether the diuresis observed is to be accounted for as the result of an increase in glomerular filtration because of elevated intracapillary pressure, or should be ascribed to diminished reabsorption of fluid by the tubules is not clear from the experiments. In any case, the experiments on dogs as well as those on rats suggest that renal extract has an especially pronounced and prolonged effect on the blood-vessels of the kidney, because the diminution in renal flow persisted for some time after the blood pressure had returned to normal (Figs. 1 and 2).

The results reported are confirmatory of the findings published by Bingel and Claus in 1910.[1] These authors, working with material obtained by the addition of ammonium sulphate to renal press juice, observed increase in blood pressure, swelling of the kidney, shrinkage of the leg and diuresis in rabbits.

Summary. Tyramine caused increase in blood pressure, diminution in renal blood flow, shrinking of the kidney and either no change

or a diminution in urine volume. This substance is believed to cause contraction of the afferent glomerular vessels.

Renal extract (Tigerstedt's "renin") caused increase in blood pressure, diminution in renal blood flow, swelling of the kidney and increase in the excretion of urine. Granting the possibility that some of these alterations are due to impurities rather than to the action of the pressor principle, the experiments suggest that the latter substance produces contraction of the efferent glomerular vessels. Constant changes in the several functions studied were not encountered following the administration of similarly prepared extracts of the liver and of the spleen.

The vessels of the kidney appear to be particularly susceptible to the action of renal extract, for the diminution in renal blood flow which followed the administration of this extract was usually more pronounced and of greater duration than was the elevation of blood pressure.

The experiments throw no light on the question as to whether the renal pressor substance is of any significance in health or in disease.

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TYPHUS FEVER IN PENNSYLVANIA.

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Typhus fever was first clearly recognized and differentiated from typhoid fever by Gerhard,[7] of Philadelphia, in 1836. Some of the great epidemics of Europe, recurring since the 16th century, have been due to it. The disease in epidemic form has never been common in Pennsylvania, although occasional outbreaks in Philadelphia have occurred in connection with the arrival of immigrants from Europe. The last outbreak recorded in Philadelphia was in 1883[16] since when no further mention is made of epidemic typhus in this state. Despite the absence of epidemic typhus in Pennsylvania and other sections of this country in the present century, students of the disease[1,4,8,12] in America have found that it occurs endemically in

certain localities under circumstances which would seem to exclude the likelihood of recent importation of the virus from abroad. Since 1910,[1] the term Brill's disease, has been used to designate the type of typhus which is endemic in this country, although the name is gradually being replaced by that of endemic typhus. The disease is now readily differentiated from typhoid fever, but in Pennsylvania[6] during the past few years another typhus-like disorder, Rocky Mountain spotted fever, has been confused with it. The purpose of this paper is to present the incidence of endemic typhus in Pennsylvania, and to report 3 cases recently studied at this hospital, in order to emphasize the salient features of the disease. Although these cases appear in the archives of this hospital as being endemic typhus, it will be seen from the following, that the first and possibly the second case are more probably instances of Rocky Mountain spotted fever.

The first report of endemic typhus in Pennsylvania was by Lewis[10] in 1911, at which time he presented 13 cases of socalled Brill's disease treated at the Pennsylvania Hospital. Six of these cases occurred in 1907, although they were not recognized as such until Brill's report in 1910. Three years later Roussel[16] (1914) published 4 additional cases and in 1931 he[5] mentions 10 more cases from Philadelphia. The above 27 cases, all from this city, constitute the incidence of endemic typhus in Pennsylvania as recorded in the literature. According to recent statistics of the Pennsylvania Department of Health[2] only 2 cases of the disease have been reported in this state since 1906, but unfortunately no data are available concerning these, except that the cases occurred in 1913 and 1914 respectively. We have presented (Fig. 1) the incidence of the disease, as recorded by the health departments[2,9,11,14,15,17,18] in Pennsylvania and the states which bound it, during the past 5 years. We believe that the incidence of the disease is greater in this state than the above data indicate, due possibly to faulty diagnosis or to failure to report the disease.

How long endemic typhus has existed in this state, and how extensive has been its spread elsewhere, is uncertain. It is known, however, that the disease is widespread among rats and is transmitted to man by the bite of infected fleas. The Xenopsylla Cheopis (rat flea[3]) is considered the principal vector of the disease from rat to man and has been shown to be most prevalent during the fall season when the incidence of typhus is greatest. During a recent survey[19] of the port of Philadelphia, it was found that 60% of all fleas captured over 19 consecutive months belonged to this species with their highest incidence during the fall months. The Norway rat, regarded as the chief reservoir of the disease in this country, was the only species represented among 2765 rats captured at that time. Since these infected vectors usually remain undetected until man contracts the disease, the epidemiologic character

and the geographic distribution of the disease is based primarily on human case reports.

Endemic typhus may be briefly defined as an acute, infectious, but non-contagious disease, usually seen in late summer and fall, showing no predilection for the lower strata of society, and is widespread among rats being transmitted to man by infected fleas. Clinically it is characterized by sudden onset with chills, a continued fever terminating usually by rapid lysis about the fifteenth day; headache, weakness, a macular eruption which appears about the fifth day on the chest and abdomen, then spreading over the upper arms and thighs, but rarely involving the palms and soles and almost never the neck and face. Convalescence as a rule is

FIG. 1.—The incidence of typhus fever, as recorded by the Health Departments in Pennsylvania and the states which bound it, during the past five years.

rapid and complications seldom occur. The mortality of the disease is about 3% with an atypical pneumonia the chief cause of death. The pathologic findings[13] are referable to the vascular system, where endothelial proliferation is followed by thrombosis and a perivascular accumulation of macrophages and lymphocytes, particularly in the skin, brain, heart, spleen, and lymph nodes.

Although the clinical course and the character of the exanthem leads one to suspect the disease, the diagnosis must be confirmed by laboratory studies. The total white count usually falls within normal limits, although a leukopenia is often seen and occasionally a slight leukocytosis in uncomplicated cases will occur. The hemoglobin and red cells do not show much variation. The urine shows changes common to other fevers. At some stage of the disease, usually by the end of the second week, the blood contains sufficient

specific agglutinins for proteus X-19, as demonstrated by the Weil-Felix reaction.

The Weil-Felix reaction is also positive in Rocky Mountain spotted fever. Typhus fever, a flea-borne infection, occurs usually in late summer and fall in urban districts. The rash is first noted on the chest and abdomen, and although it frequently spreads to the upper arms and thighs, it seldom involves the palms and soles and almost never the neck and face. Rocky Mountain spotted fever, a tic-borne infection, is most commonly seen in the late spring and summer months in rural communities. The rash makes its first appearance on the wrists and ankles, with rapid extension over the entire body including the palms, soles, neck and face. If necessary, guinea-pig inoculation and cross agglutination tests are available through the Public Health service.

Since typhus fever is self-limited, and specific therapy unknown, symptomatic treatment and supportive measures must be relied upon. Various attempts at prophylactic vaccination have been made, but the use of a living virus as a vaccine has been proven dangerous. The obvious prevention for the disease, since it is carried by rats and transmitted by rat fleas, is the destruction of rats and rat harbors.

We have included in the following case reports the pertinent features of the histories and the positive physical and laboratory findings. Blood and urine cultures as well as repeated Widal agglutinations were negative in each instance (Fig. 2).

Case Abstracts. Case 1.—J. M. (34–17543), a 19-year-old white male, was admitted to this hospital on June 18, 1934. On the day before admission he complained of a severe headache, generalized body pains and soreness of the eyes; followed on the next day by sore throat, fever, diplopia, tinnitus, stiffness of the neck and a definite convulsion. The patient admitted having been bitten by tics about 2 weeks prior to his illness while working in the immediate vicinity of his home, which was approximately 35 miles from Philadelphia.

Physical examination revealed an acutely ill boy with a profuse pink maculopapular rash over the entire chest, abdomen and extremities but not involving the soles, palms, neck and face. There was moderate redness of the throat and some neck rigidity. After admission, the pyrexia, rash, and neurologic symptoms persisted until about the fifteenth day of the illness, at which time the rash had completely disappeared and the elevation in temperature subsided almost by crisis. The patient made an uneventful recovery being discharged on July 15, 1934.

Case 2.—W. L. (35–19833), a white male, aged 53, was admitted on May 12, 1935. The present illness began 6 days before admission, with pain in the left shoulder, followed in 2 days by general malaise, fever (102°), severe headache and backache. On the fourth day of illness there appeared a rose-colored rash involving the chest and abdomen. The pyrexia (102–104), headache and rash persisted until admission on the sixth day of the disease. He had not been out of Philadelphia for several months prior to his illness and denied any knowledge of contact with tics or any rat infestation in his home or at his place of business.

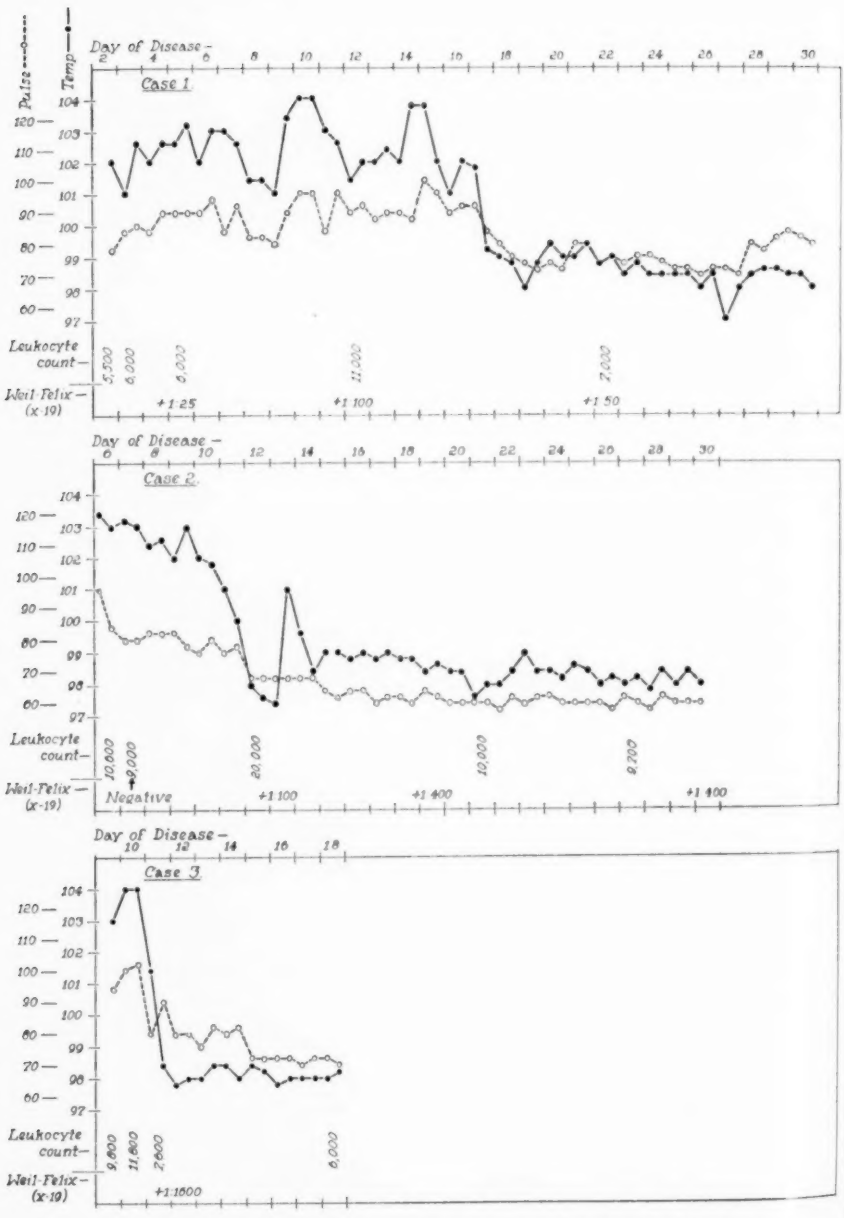

FIG. 2.—Showing days of disease, temperature ranges, pulse rates, leukocyte count and Weil-Felix agglutination reactions during hospitalization.

On physical examination the patient did not appear acutely ill. Over the abdomen, trunk, chest, and shoulders was a diffuse, pink, macular eruption which faded on pressure. The throat was markedly injected and the liver slightly enlarged. Following admission the symptoms continued and on the twelfth day of the disease, the patient experienced generalized abdominal pain accompanied by a sudden fall in temperature with an elevation of leukocytes and rigidity in the right abdomen. This initial drop in temperature was followed the next day by an elevation reaching 101°, with physical signs of fluid in the left chest; a finding which was confirmed by Roentgen ray examination. This upset was attributed to a pulmonary embolus from a small mesenteric thrombosis. The rash had completely disappeared by the fourteenth day of the illness. Following the above complication, the patient improved gradually and at the time of his discharge, June 5, 1935, both lung fields were clear and his usual state of health resumed.

Case 3.—G. S. (33,13215), a white woman, aged 48, was well until February 15, 1936, 9 days before admission, at which time she complained of weakness, generalized body pains, severe headache, profuse sweating, chills and fever. Five days later these symptoms were followed by a rose-colored rash involving the abdomen, chest and upper arms. The patient had remained in Philadelphia for over a year preceding her illness and although she denied rodent infestation of her home, subsequent investigations proved otherwise. We were unable to capture any of the rats on the premises, but the patient's family admitted having seen rather large rats in the basement of their home.

Physical examination revealed no evidence of acute distress. The throat was slightly injected and the abdomen and chest were covered with small pink macular lesions. After admission the patient continued to have an elevation in temperature, sweats, and severe headache. The rash had completely disappeared by the eleventh day, at which time the pyrexia subsided almost by crisis. The patient was discharged on March 3, 1936, after an uneventful complete recovery.

As stated above, the first and possibly the second case represent instances of Rocky Mountain spotted fever rather than endemic typhus. In the first case, the illness occurred during June in a rural community with a history of tic bites followed by rather severe cerebral manifestations. The illness in the second was during the spring although the patient lived in an urban district and denied any history of contacts with ticks. Both cases, however, lacked the typical distribution of the rash as well as the necessary laboratory studies to differentiate between endemic typhus and Rocky Mountain spotted fever. It is probably that certain cases reported in the past as Brill's disease or endemic typhus would now be considered as Rocky Mountain spotted fever. Since we lack the necessary laboratory data for an accurate differentiation of these typhus-like infections, we are including all cases in this report with the diagnosis of endemic typhus both from the literature and the records of this hospital. Of the 30 cases with this diagnosis, 29 occurred in this city. The data at hand indicate a focal distribution in Philadelphia, but sufficient information is not yet available for an accurate delineation of infected localities within Pennsylvania.

Summary. 1. The incidence of endemic typhus in Pennsylvania as recorded in the literature is presented.

2. A comparison is made of the number of cases reported to the health department in this and surrounding states during the past 5 years.

3. Three cases studied at this hospital and diagnosed as endemic typhus are reported.

4. The differential diagnosis between the typhus-like diseases in this state is discussed.

5. Physicians should be aware of the presence of this disease in Pennsylvania, especially in Philadelphia, during the late summer and fall months.

6. The importance of reporting all cases as an aid in the epidemiologic study of the disease is stressed.

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DISEASE AND THE NEGRO.*

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Observation of the negro's body brings to our attention many points wherein he differs from the white man. The colored skin, the tightly curled hair, the protruding eyeballs, suggestive of hyperthyroidism, are some of these points. The silhouette of the negro's head with the slanting forehead, tendency to enlarged frontal sinuses

* This contribution is the foreword of a book of the same title upon which the authors are at present engaged.

and heavy protruding mandible brings out other well-known characteristics. Pictured by the Roentgen ray, the bones of the negro can commonly be recognized as such by the thickened walls of the calvarium, the narrow pelvic outlet in the male, and the bony protuberances on the humeri and pubic arches which serve as points for muscle attachments.

Contrary to the general belief, the hands of the negro are frequently smaller than would be expected when we consider the size and strength of his body. Full-grown men of this race of unusual power and muscular development are seen presenting the hands of a 16-year-old boy. It has been an observation in the Employees Hospital for years that the so-called artistic hand with its slender tapering fingers is a common possession of negro women. These variations in form are all structural differences guided no doubt by complex glandular activities to which at the present time we have no key.

When we consider the two races in motion, we find more important differences. The negro is more lethargic in his movements. His gait inclines toward a shuffle. There is a slackening of the knee-joints suggestive of a man walking with skis. The force of gravity seems to act with greater power upon the negro than it does upon the white. He rarely rises upon his toes. His activities in the prize ring past and present bring out this point in a striking way. In the parlance of pugilism all great negro fighters have been "flat-footed fighters." They have produced results by shuffling in toward their opponents bearing their whole weight upon the flattened foot.

We have never been able to believe that the diseases of the two races as such, differed in any essential detail. Many thousands of laboratory tests performed here during the past 18 years have produced similar results in the 2 races. Throughout the whole gamut of diagnostic research as represented by basal metabolic estimations, blood chemistry determinations, and the other various techniques which are commonly employed, the normal findings have been identical. Differences found in the negro as in the white have been differences due to his age, sex, economic condition and other factors. We have never been able to find any true racial differences. Nor have we been able to find in the work of others similarly engaged, proof of any such differences.

Nevertheless, it has been the observation of those who have directed their attention toward this problem, that the disease patterns of the two races differ in many respects. Indeed, if our perceptions had not been lulled by a constant repetition, the differences in both morbidity and mortality rates relating to sickness as it occurs in the two races would be regarded as startling. This has been common knowledge for some time. So far as we know, no explanation has ever been presented which suggested the existence of a common denominator. It is true that obvious conclusions

have been drawn from separate instances. The sexual promiscuity of the negro has led to his syphilization. The sparsity of his diet has led to outbreaks of pellagra. These are merely explanations of episodes. They cannot solve to anyone's satisfaction the broad problem. Such relations deal only with separate entities and it will be noted with positive factors only. At best, they are connected with the increased occurrence of disease which, as we shall see, portrays only a part of the picture. The problem under discussion is more intricate than that.

We have felt that there was some common cause which operated both toward the increased frequency of some diseases, and the diminished frequency of other diseases among our colored patients. Early in our search we became aware that consideration of disease in the negro entails an oblique consideration of disease in the white man. We have felt that through this obliquity of approach, profitable implications might be unearthed regarding the latter's problem also. Not that we need any such goad. The search, if confined to the negro alone, would require more intelligence than any one set of observers could possess.

Since a search of all clinical and laboratory records proved barren of results in producing evidences of true racial differences in regard to disease, we turned to other sources for enlightenment. To guide us in this quest has been the impression, a persistent one, that the search has been founded upon too narrow a base. The mental side of the picture has not received the attention it deserved. The attitude of the colored patient toward his disease, whatsoever it may have been, has not been elucidated. A circumstance of common occurrence, encountered in our daily routine, has kept recurring to our minds. Whenever we engaged in conversation with the type of negro we see in our wards, we became aware that great as were the physical differences between us they were no greater than the mental differences brought out by this simple form of human contact. This constant experience with the sick negro has convinced us that nowhere in the comparison of the psyche of the two races are there more important or momentous differences than in the ideology which each possesses regarding disease.

If we are presented with the opportunity of comparing sick white people and sick colored people, we are struck with the fact that there are widely different patterns of disease in the two races. These patterns differ not only in the circumstance that each race has its own set of diseases common to it, but also the degree of disability created by any specific type of disorder shows a variance in the two races. When we compare the cultural levels of the two groups, this is not at all surprising. The white people reflect an attitude conditioned by a greater knowledge of the subject of human sickness, incomplete though it may be.

Through their experiences in childhood, by word-of-mouth tradi-

tion which they have absorbed from their parents and older associates during their adolescence, they have at least a working knowledge of what it is all about. They have heard all the common forms of sickness described and defined. Since this subject is so often a matter of family discussion, their information from this source alone is considerable. Most of us can look back into our childhood and recall that our ideas of disease received their first definitions at that time. These definitions have persisted in the minds of many to color that side of their mentality in later life. To some the recollection of a member of his family suffering from the tortures of an acute appendix with the resulting spectacular surgical relief, remains as one of the vivid memories of their childhood.

Later as the medical profession extended its vocabulary, and its knowledge became more and more public property, ulcers of the stomach and duodenum, with their possible complications, goiter, diabetes and other sinister names took their place in the public consciousness. Ideas upon these and similar emergencies became a part of the white person's thinking life with the certainty that each one might apply such possibilities to his own instance when the occasions arose. We may take it for granted that no human being who had heard of such horrors could become aware of their proximity in the person of someone near and dear to him without the possibility of his own vulnerability becoming apparent to him. This type of knowledge, often highly inaccurate in character, became a part of the folklore of white people with any pretensions to education. Indeed it became a part of everyday education well nigh as important as the ability to read and write; for without it one was left out of the circle when discussions arose on a subject of such universal interest.

When an attack of sickness came to any white person, the very human question arose in his mind as to the identity of his complaint. As time went on and his opportunities for education along this line presented themselves, his view of the disease problem was constantly being widened, new disease names were added to his list. As the discussion of diseases progressed in the public mind through newspaper articles, advertisements, and of late through the radio, the minds of white people as a group achieved a broad scope in the consideration of the all-important matter as to what it was that was making them sick. This educational process has its good and its evil points.

Through the vigilance which it has created, many hasten to the doctor early in the course of their malady and are thus saved the dangers of delay. In a word, white people of any reasonable degree of intelligence pay at least as much attention to the state of their health as the subject merits. This is a valuable contribution to the life prolonging scheme of their lives. It is viewed as laudable and praiseworthy whenever the patient is found to be suffering from

what is known to the medical profession as an "organic disease." Such disasters it is common knowledge are amenable to cure just insofar as they are permitted an early recognition. Malignant growths, pulmonary tuberculosis, and many other thorns in the side of humanity fall into this category. If we see them early we feel that we can do them the maximum of good.

It is a fact well known to the profession, however, that all this educational campaign by which the laity have been acquainted with the ills of the flesh has been by no means an unmixed blessing. With increasing frequency we believe as time has gone on many unfortunates have been brought to such a state of vigilance in regard to the state of their health, that they are constantly on the *qui vive* toward those signs and portents which accompany the life processes of every human body. These men and women note with apprehension every variation in the rate of their heart beat. They watch with dread the changing pressures in their hollow viscera. They magnify all the physical and physiologic changes which mark the human body striving to maintain its equilibrium. According to the degree of education which they have obtained in a haphazard way they attempt to identify these trivial things as diseases. This one has a gastric ulcer, this one a goiter; in their minds at least.

This is the type of patient who outnumbers many times over the patients who seek medical advice suffering from some organic disease. To them, certainly, the vigilance in regard to their well-being created by a generation of education along medical lines has not been a boon. When we meet these people, we are immediately aware that they all have an explanation for their sickness. They have a name for their disease. More often than not, this name bears little if any relation to the truth of the matter, but they have given it a name nevertheless. Fifty years ago the nomenclature of disease was much simpler. The minds of the laity were satisfied with clichés which would never pass muster today. People in that time had "heart trouble" or "kidney trouble" or "Bright's disease" and the dreaded "dropsy." With these simple trade-names they must have been able to satisfy their minds. The physicians of the day had little more to tell them; indeed if they were honest men they must have questioned the truth of even these bare disclosures.

Today our white patients demand more from us than the simple statement of a condition. They demand proof: Roentgen ray diagnosis, chemical tests, blood examinations and what-not. They must have faith in these procedures as they are always willing to pay for them. It is this same attitude of eternal vigilance regarding their health that makes white people skeptical when all too often the examination performed with its expensive ritual, confounds the ideas which they have formed as to what ails them. If it is not a cancer that they have, then what is it? The symptoms from which they suffered, and all that they had read upon the subject and all

that they had heard, had led them to the conclusion that a cancer was what they had. It may be that they have learned too much about the problem of disease, or that the manner in which they have learned has brought them only misfortune.

When we cross the hall into a ward of sick negroes, we find that we are entering another world. Whatever may have been the early education of the negro in the definition of disease, it has left few marks behind it. If they are aware of the ills to which the flesh is heir they never mention the subject. Though we have seen thousands of negro patients in the past 15 years, we have yet to see the first one to suggest that he or she may be suffering from that bane of the white folks, an "ulcerated stomach." If they have heard the words they have long since forgotten them. Their attitude toward the organs of the body is an attitude that is free from strain and antagonism. Their attitude toward their own physiologic processes is marked by a simplicity and common sense that is far above that of the Caucasian. In the natural course of events they must have read some of the modern advertising on how to maintain their health at a proper level.

Radio commentators must rarely have consumed some of their time addressing them on the subject of vitamins and the ills which were bound to follow if their advice were not taken. The seed so far as we have been able to observe has fallen on barren soil. As a group they have refused to become concerned about the varying activities of their digestive organs, matters which are of the deepest interest to their white contemporaries. The negro takes such things as a matter of course. He lives at peace with the various parts of his body, to an extent that is only approached in the best balanced of the whites. His stomach is his friend, his intestines are organs to be left alone and not tampered with by all sorts of maneuvers. Leave such things alone, is the negro's point of view. The attitude of the negro toward all forms of sickness is one of disregard. He pays them no attention, and thus manifests his belief that in the end all such troubles will disappear.

It is this conviction on the part of the negro which is the determining factor in conditioning disease patterns as we see them affecting the two races. The great mass of symptoms without any underlying discoverable lesions which brings thousands of patients to the physician suffering from what we call "functional disorders," serve no such end in the negro's instance. He takes no such interest in the physiologic minutiæ of his life as does the white. A pain in his stomach is just that; his mind is free from the multiplicity of horrors which creep unasked into the white brain whenever such a minor event threatens a white body. He can hardly consider himself as developing the deadly pains of appendicitis when he has never heard the expression or has forgotten it long since if he ever did hear it. He is spared the fear of many diseases because they have

never taken definition in his mind. Since his brain holds no image of them he cannot suffer from them.

When we look into the matter we shall find that the occurrence of what the profession calls "organic disease" is much higher in the negro than it is in the white. Not only are such misfortunes more common, but they are met in a more advanced stage. When we encounter such diseases as pulmonary tuberculosis, carcinoma, exophthalmic goiter, we find that they are disclosed as a rule only after long periods of progress. Here the disregard which the negro pays toward all forms of disease has acted to his detriment. Had he a tithe of the vigilance which the white man displays in such matters it would be greatly to his advantage.

The strength of his position is best shown when we step into that vast field of vague and indefinite symptoms personified by the type to which has been given the name of "neuro." From the terrors of this man's days with his vertigo, headache, constipation, flatulence, air-filled stomach and intestine, and anal pruritus (to name only a few of the more common symptoms) the negro is free. He is rarely found in that vast army which pauses momentarily in the physician's waiting-rooms, on their way to be cured by the quacks. All of our previous experiences lead us to the belief that from this collection of human misery, the negro has been shut off by the state of his mind. Not that he does not suffer from subjective symptoms, the same in fact which make the white man miserable, but that he pays them no attention. He has no dreaded names to give them. He has no store of ideology which provides some horror to identify with some mild abdominal complaint. We might call such a state of mind only a proof of the valor of ignorance, but to many sufferers in white skins it would be a blessed ignorance indeed.

We have always tried to bear in mind that the problem of the negro in sickness represents merely a part of the problem of his life as a whole, differing from the main pattern merely in detail. We believe, however, from what we have seen that the negro entertains a true disregard for disease patterns for reasons which we have endeavored to make clear. This disregard is not identical with his racial reticence, which conditions every relation which he has with the whites. This reticence colors his thoughts and restrains his conversation frequently to monosyllabic replies when conversing with the other race. When dealing with the white man the negro is on the defensive, and well he may be. He seems to be under the impression, which is well-founded in truth, that many white men would not engage him in conversation, or indeed pay him any attention at all, if they did not have some ulterior motive to serve.

Years of unfortunate contacts have led the negro to be on his guard with many Caucasians—not only to be on his guard, but to make a persistent study of the personalities of such members of the dominant race as his daily routine touches. In a way, the negro has

all the advantage when such contact takes place. He knows all about the white man: his habits, tastes, virtues and vices, and he has formed a shrewd estimate of his personality. This knowledge, however, he only dares to use in a negative way. He knows that not always is there an equality of footing, and all that he has become aware of in regard to the white man he will be able to employ chiefly to guide him in the protection of his own interests.

White people who have the name of dealing fairly with their negro associates have few difficulties with the race problem. What one negro knows about them every negro in the community knows. The white people who in the negro's judgment have been unreasonable or unjust, he simply avoids. If he has to enter such employment, he endures it for only so long as is necessary and then departs as silently as the Arab. We have never encountered a negro who held to the belief that parting was a sweet sorrow. When dealing with the white man, the negro is frequently playing a part—the part which in his judgment is most pleasing to his white audience. If such entails smiles, laughter, rolling of the eyes in traditional negro manner, such antics are forthcoming. If he concludes that restraint best serves his purpose, then it becomes evident. He can be all things to all whites. The negro occupies an anomalous position in society. In regard to all the modern means of advancing himself he lags behind. This is due not only to his enforced inferior social level but also to his lack of knowledge of modern business methods. He lacks the ability to pursue objectives over long periods of time, and he is hampered by his ease of distraction. In a word, he is at a great disadvantage in this world which the white man has so cunningly molded to his own ends.

In other ways the negro is far ahead of his racial rival. For one thing he is far shrewder. He is more observant of his adversary. While we believe that the negro views the motives of his white associates with skepticism, this feeling does not destroy his interest in the objects of his emotion. This attitude is aptly shown by the manner in which he cajoles us into doing some of the things he wants us to do. While the issue is taking form he achieves a part at least of his purpose. Unknown to them the negro is constantly cozening his white associates and we believe enjoying it.

He shows his true feelings toward us by his reticences. Invariably he tells us just what he thinks would be good for us to know and no more. Though our negro servants have learned all the intimate news of the neighborhood long before we have become aware of anything of importance having happened, they impart this knowledge to us piecemeal. It is measured out to us in what they consider proper doses, as we break news to children. Strange to say, always this information which they convey to us with appraising eyes, turns out to be founded in fact. It is never exaggerated and many times has been toned down at its source in order that we

should not be shocked by the too sudden acquisition of knowledge. It would simplify our problem if we could theorize something after this fashion:

Certain diseases which are common among whites occur infrequently among negroes. This disparity is due to the habitual disregard which the negro displays toward all forms of disease. We may then assume that only those diseases tend to appear among the negroes which are impervious to human disregard—diseases against which emotional defenses are inadequate. If the white race employed the same emotional defenses, his history of disease incidence would parallel that of the negro.

While we believe that in the main this thesis is true, it is certainly not subject to proof in its entirety. Several disease patterns occur with great infrequency in the negro, but are common in the white race, concerning which up to the present at least, no psychogenic origin has ever been suggested. It may be that in spite of present difficulties this theory may be more fully proven; stranger things than this have happened in the field of medicine in the past two decades. What we believe at present, and we venture to say it is self-evident, is that the study of disease in the negro will advance rapidly all our knowledge of the psychogenic factors of disease as it occurs in both races.

The two cultural levels are so different that two entirely different taking-off places are afforded us in our comparative study. In time this opportunity will be lost to us. Already in certain communities where the two races mingle more freely than they do here in the South, the attitude of the negro toward disease is becoming like unto that of the white. Those who have read Frederick Steigmann's[1] analysis of gastric ulcer occurring in the two races at Cook County Hospital in Chicago, will recall the implied query as to why negroes must spend years in that city before they develop this disease. We must admit that this was no puzzle to us. It took the newcomer that period of time to have formed in his mind just what an ulcer was, and what it might portend. The rest was simple enough.

In time we in the South shall meet similar changes in *our* clientele. The primitive detached attitude toward disease and the naive courage of the negro are bound to fall before the type of knowledge that is being spread abroad. The radio and the printed pages of advertisements will play their part in the story. Through these two sources the American public derives the greater part of its medical knowledge and the negro is bound to be engulfed. We can reconcile our minds to that conclusion only by trying to believe that the present unfortunate state of the public knowledge in regard to all forms of sickness is merely a necessary step in our progress toward better things.

Much time and effort has been expended in discovering a genotypic form of disease which would distinguish such variations from

health as they appear in the two races. Little if any progress has been made in this direction. The reason is plain. Such efforts have confined themselves wholly to physical factors, and have disregarded the psychologic element in the problem. As we have already stated, there is no appreciable difference in the working of the physiology of the white body from that of the black. It would be opposed to all reason to expect such differences to appear out of a clear sky when the two races enter what we term a period of sickness. What has not been taken into account is the fact that each race carries on through its illnesses the same personality characteristics which distinguished it in health. That is true of the white man as it is true of the black man.

The latter type only concerns us in this study. If we would truly seek for a genotypic form of disease in the negro, then we must take the sum total of his personality, and not alone the physical workings as they are shown in his body. Whatever has been an element of strength remains with him when he takes to his bed. The same qualities of weakness which hampered his progress in his work-a-day life abide with him when he is under the care of his doctor. It cannot be too often repeated in this search for cause and effect in the instance of the sick negro that with him, as with all men, sickness is not a separate life into which he enters shutting all the doors of his past life behind him.

Nor a condition into which for some unknown cause he is born again with a novel but stereotyped personality. The period of the negro's sickness is nothing more than the progress of his previous life, with all its encumbrances whipped up to a greater speed by factors such as fever, delirium, malnutrition and all manner of physical urgencies. Viewed in this light, we have no difficulty in discerning a true genotypic form of disease in the negro. This form is not confined to any discrete infection, but molds and shapes the pattern of whatsoever type of disease the negro encounters.

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THE RELATIONSHIP OF ORTHOPEDIC SURGERY TO INTERNAL MEDICINE.*

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In its broadest concept, modern orthopedic surgery encompasses the problems of the skeletal structures and the mechanics of the

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viscera. Functional or organic involvement of these structures is of frequent occurrence in the daily routine of the general practitioner or internist, who has been trained to examine patients with a consciousness of the high incidence of orthopedic problems. It is decidedly less frequently observed by those who examine patients in the recumbent position or who fail to have patients strip further than the waist and whose inquiries do not include observations concerning posture, the mechanics of the lower back and feet, the shoe, the corset, the competency of the peripheral vascular system, the type of gait, occupational trauma, the type of chair or mattress commonly used.

The internist who recognizes the frequent occurrence of skeletal disturbance will summon the modern orthopedic surgeon with increasing frequency and satisfaction. The orthopedic surgeon who retains the broad viewpoint of the physician and is not afflicted with the shaft vision of the specialist will, with increasing frequency, recognize the advisability of summoning the internist to assist in the complications that so frequently either precede, accompany, or follow orthopedic conditions, most particularly those concerned with infection and metabolic derangement.

In private practice the approach to an ideal interrelationship seems more frequently fulfilled. Hospital practice is handicapped by the segregation of many of the orthopedic surgeons in orthopedic hospitals and in the general hospital by the lack of recognition of the vast importance of the orthopedic service. Your program this evening affords an opportunity for the interchange of ideas between orthopedic surgeon and internist.

Acute Arthritis. The patient with acute arthritis commonly consults the internist. In hospital practice such patients are usually admitted to the medical wards. All too frequently such patients are treated exclusively by the internist, whereas valuable information and assistance should be obtained from the orthopedic surgeon. In the acute arthritides characterized by effusion, aspiration of the joint is an invaluable diagnostic and therapeutic procedure. We internists are altogether too timid about this procedure which, if done by the orthopedic surgeon, should be wholly without risk. In the coccal infections (gonococcus, pneumococcus, streptococcus and staphylococcus), the diagnosis may remain in doubt until aspiration is performed. The laboratory findings may then indicate clearly the therapeutic regimen, both constitutionally and locally. In rheumatic fever the aspirated fluid is of negative diagnostic importance, but its removal often gives prompt and dramatic relief from pain and precludes the necessity of forcing the analgesics which will sooner or later disturb the digestive system and hence undermine the nutrition of the patient.

In acute arthritis the internist is prone to use rest, and either

inadequate or excessive immobilization. Inadequate immobilization results in excessive pain, where snug splinting, or the application of plaster or traction might give complete relief. Prolonged immobilization may result in deformity, stiffness, limitation of motion, atrophy, and even ankylosis.

With the possible exception of sulphanilamide, now under investigation, specific drug therapy has succeeded only in giving symptomatic relief. The tendency of all of the forms of salicylic acid to result in digestive disturbance, the fear that the derivatives of cinchophen may not only upset the digestion but cause varying degrees of damage to the liver cells, and the occasional toxic effect of amidopyrine upon bone marrow, impels the wise physician to utilize drugs as infrequently as possible. One might paraphrase the old axiom that he is the wisest physician who knows the greatest number of useless drugs.

Where the orthopedic surgeon has been first summoned to deal with the problem of acute arthritis, the responsibility must be shared with a competent internist. The latter must investigate the general condition of the patient, most particularly with regard to his cardiovascular status, and serve in a judicial rôle to interpret the reports and recommendations of the various interested specialists.

The present advances in the technique of artificial hyperpyrexia elevate the modern physio-therapist to a position where the orthopedist and internist, in close coöperation, may summon him with whole-hearted and hopeful expectation of a therapeutic result. The strenuous character of this therapy and the necessity of including care of the mechanics of the involved joint can be best accomplished by the close coöperation of physiotherapist, internist, and orthopedic surgeon.

The management of infectious arthritis is essentially in the hands of the internist. The search for the infective focus must be intensive. Abscessed teeth must be removed, infected tonsils must be enucleated, the nose and accessory cavities must not only be examined visually and radiographically, but a diagnostic lavage of the antra must be performed by an exceedingly competent laryngologist. In the absence of other findings the nasopharynx is to be scrutinized particularly for small pockets of pus in lymphoid tissue, as in the Thornwaldt abscess. The reproductive organs must also be investigated. This should include prostatic massage in the male and visual examination of the cervix in the female. The eradication of the infective focus should be performed promptly and as soon as the temperature approaches normal. There is no necessity for waiting weeks or months fearing to activate the lesion.

It is in infectious arthritis alone that I believe autogenous vaccines are of genuine value. The necessity of dealing vigorously with foci of infection is augmented by the fear that the infectious arthritis

may be a precursor of rheumatoid arthritis. Whilst many believe that the latter is an end-stage of the former, I am of the opinion that the two may be differentiated by the constitutional phenomena to be described later.

Of the metabolic acute arthritides, gout is the most frequently observed. It is my experience that the frequency of gout, including the gouty diathesis, is greatly underestimated. Where patients complain of any type of skeletal pain, including arthritis, periarthritis, synovitis, fibrositis, myositis, myalgia, or even recurrent phlebitis, a search for deposits of urates, a determination of the blood uric acid and, finally and most important, the therapeutic test should be initiated. In any instance where symptomatology is relieved by adequate dosage of a potent preparation of colchicum, by which I mean sufficient to cause diarrhea, the diagnosis of gout or gouty diathesis should be made. The more frequently the therapeutic test is done, the more frequently will the diagnosis be made. Such patients should be managed by the indicated dietetic principles, by maintenance doses of colchicum, and by the weekly or fortnightly exhibition of the time-honored calomel-saline sequence.

In acute traumatic arthritis, the tendency towards hemarthrosis and subsequent stiffness or ankylosis necessitates early consultation with the orthopedic surgeon for the purpose of aspiration and the early institution of motion. Persistent or repeated bleeding suggests the hemorrhagic diseases such as hemophilia or avitaminosis as in scurvy.

If traumatic arthritis is recurrent or if the trauma seems insufficient, investigation into the mechanics of the joint for a local etiologic factor should precede the discharge of the patient.

Chronic Arthritis. In dealing with chronic arthritis, the closest coöperation between internist and orthopedist is imperative. In the specific arthritides, such as syphilis and tuberculosis, the management is extraordinarily one-sided. For the most part, the luetic is under the care of the internist who must never neglect, particularly in tabes, to prevent deformity by adequate mechanical support and reëducational exercises. The patient with tuberculous arthritis is usually handled by the orthopedic surgeon who, at recurrent intervals, should insist on medical consultation, particularly directed to the detection of extension of infection in other parenchymal structures, to the presence of dissecting abscess or amyloidosis.

In the non-specific chronic arthritides, therapeutic chaos can only be prevented by the insistence, whether by the orthopedist or internist, on a preliminary survey by the various physicians concerned.

The necessity of differentiating between hypertrophic osteoarthritis and rheumatoid or atrophic arthritis need not be stressed in this place. It is my opinion that hypertrophic osteo-arthritis and

spondylitis are essentially metabolic disorders. Trauma resulting from faulty mechanics is probably an important factor in the production and the continuance of symptoms. If uncorrected, it may lead to increased local or distant mechanical difficulty.

In hypertrophic osteo-arthritis, intelligent coöperation between orthopedist and internist should result in complete relief of symptoms almost without exception. The task of the internist is to reduce the weight of these patients, who are ordinarily obese, administer thyroid substance in dosage sufficient to raise to normal and maintain at normal the metabolic rate, inject potent estrogenic hormone at the climacteric, correct constipation and any other obvious metabolic abnormality. It is the function of the orthopedist by corrective exercises, the use of corsets, belts and other forms of mechanical aid, to coöperate with the internist in the therapeutic regimen. There are several practical points in the management of these patients which I wish to stress. The administration of thyroid must be checked by frequent estimations of the basal rate. It is essential, particularly for the orthopedic surgeon, to be certain that the rate is a basal rate and not merely a reading of oxygen consumption, performed under dubious circumstances by a technician. I have learned to look with grave distrust upon metabolic rate determinations as reported from commercial laboratories. The dosage of thyroid is a distinctly individual experiment. Any thyroid product put up by a reliable pharmaceutical house may be employed. It is the first task to raise the metabolic rate to normal and the dosage is the amount that is necessary in that particular individual to obtain the result desired. Certain patients will be exceedingly sensitive—others exceedingly refractory. *A priori*, I know of no way of distinguishing the two. In a rough way, 1 to 2 gr. daily may be the dosage for the patient whose rate varies between 0 and −10%; 2 or 3 gr. between −10 and −15%; and 3 to 5 gr. where the rate is below −15%. Having raised the basal metabolic rate to normal, the dose must then be reduced to a maintenance, for continuance of the corrective dosage will lead to toxic manifestations. Overzealous therapy may result in the production of toxic symptoms from the sudden change in tempo in patients whose basal rate is still on the minus side.

Another practical difficulty arises in the performance of corrective exercise. It is the greatest exception to find a conscientious patient who will do corrective exercises regularly without supervision. The cost of supervised corrective exercise today is far beyond the means of even the average patient. The physiotherapists who give corrective exercises rarely do good massage. It would seem to me worth while for you who are in active orthopedic practice to establish some central institution where corrective exercise and massage could be adequately performed for a moderate

fee. I am inclined to the belief that one of the reasons for the popularity of chiropractors and osteopaths is the failure of the medical profession to provide this type of service.

In patients with osteo-arthritis, it is my belief that no other procedure should be incorporated in the regimen unless the lesion is obvious, or the symptoms fail to respond to therapy, or if they recur despite therapy. I am opposed to the promiscuous extraction of teeth, or the enucleation of tonsils, or specific therapy directed to the sinuses, or the injection of protein or "specific" vaccines or drugs, or faddist diets, unless the indication is perfectly obvious and apparent, or the patient has failed to respond to the approach *via* mechanical measures and the correction of metabolic abnormalities. I would not oppose the removal of an obviously abscessed tooth or of tonsils which are grossly purulent, or which have been the site of peritonsillar abscess, or where there is a clear history of onset or exacerbation of the joint symptoms following tonsillar infection, nor would I oppose therapy directed to an obviously infected accessory nasal sinus; but I think it is incorrect and even reprehensible for dentists to advise and perform extractions with promise of relieving or curing arthritis, or for laryngologists to remove tonsils merely because the patient has joint pain, or for prostatic massage to be indulged in for that same reason. Vaccine therapy is of no value in this type of arthritis. Non-specific protein therapy may be of temporary value, but is probably not worth the pain and discomfort of administration. Physiotherapy by means of electrical apparatus, including short wave, is probably not worth the trouble or expense. The various faddist diets, such as the alkaline diet, low protein, low starch, low carbohydrate, or the so-called Hay diet (which separates proteins and carbohydrates), are all without scientific basis or practical result.

In classic rheumatoid arthritis, however, the point of approach is wholly different. Neither the etiology nor the pathogenesis of this discouraging and crippling disease seem adequately explained today by any of the theories or data available. While we can give the patient with hypertrophic osteo-arthritis every assurance that we can obtain a satisfactory therapeutic result, we are forced to confess that in the rheumatoid arthritides our prospect of significant accomplishment is in inverse ratio. The ominous spectre of the progressive deformity makes it imperative that the physician first consulted in rheumatoid arthritis obtain the closest coöperation of all available specialists and arrange a therapeutic problem that is immediately as inclusive as possible. Infected or even suspicious teeth should be extracted, the tonsils should be enucleated, the sinuses should be investigated, and not exonerated until diagnostic antral lavage is performed, cultures should be obtained from foci, vaccines should be prepared and administered, focal infection should

be sought for and eradicated in the genitourinary passages, and no stone left unturned by the specialist group in seeking and removing any possible causative agent. It is the function of the orthopedist, in the active stage of the disease, to prevent deformity and ankylosis by the earliest possible use of corrective mechanical devices, early massage and passive motion, and later to institute active motion and corrective exercises. The functions of the internist are manifold. The sufferers from this disease are typified anthropomorphically and psychologically. Ordinarily one deals with a patient who presents generalized visceroptosis, organ inferiority, and an autonomic imbalance with characteristic vasomotor instability. The resistance of these patients must be enhanced by the use of a high calorie diet rich in vitamins and the various organic elements. If there is any doubt about the absorption of the latter, the vitamins should be artificially administered by mouth or even parenterally, and augmented by the use of direct sunlight or ultraviolet radiation. Where, as so frequently occurs, secondary colitis develops, the absorption of the vitamin products and the minerals, particularly calcium and iron, may be insufficient; under which circumstance, transfusions and the injection of soluble preparations directly into the tissues must be practised. Whilst my experience is limited, I am inclined to believe that this dread colitis, which so commonly depletes the sufferer from rheumatoid arthritis, may possibly be prevented by the use of a tight abdominal binder opposing the distention and ptosis in the atonic bowel.

Though it may seem a far cry to you who are interested primarily in organic medicine, I am quite convinced of the important rôle of the psyche, both as an accessory etiologic factor in the onset of rheumatoid arthritis and as a potent factor in the course of the disease. Situational difficulties and internal conflicts attending the onset of the disease will usually be uncovered, if a sympathetic rapport exists between doctor and patient. The correction of the psychologic situation may prove to be an important factor in the management of the patient. In the course of the disease, with the protracted therapy, the disappointments and the remissions, the morale of the patient must be maintained. It is impossible to sustain nutrition or perform adequate corrective exercise in a disgruntled and disheartened individual. It is as necessary to splint the psyche as it is to use mechanical appliances on the troubled joint. The physician who neglects this aspect in therapy is doing a serious injustice both to patient and self.

How much is actually accomplished by specific therapy in rheumatoid arthritis, is, as yet, unknown. The disease tends to progress through remissions and exacerbations to an arrested phase. Usually the patient, and often times the observer, will be tempted to attribute any accompanying successful result to the concomitant therapeutic

measure. In all likelihood the meticulous protracted attention of the orthopedic surgeon and the equally undramatic, but sympathetic, general constitutional and psychologic care by the practitioner are the more potent, but less featured, therapeutic measures.

In the arrested stage of rheumatoid arthritis, the orthopedic surgeon comes into his great glory—for here, once the disease has been surely and certainly arrested, the alleviation of symptoms, the correction of deformity, and the rehabilitation of the patient by indicated procedures, either fusion or arthroplasty, rank amongst the great surgical triumphs of modern times. Equally superb is the extraordinary teamwork and technical skill that has been evolved by the orthopedic surgeon. Infection is no longer countenanced and operative reactions to prolonged and gigantic procedures are virtually negligible.

In rheumatoid arthritis, as in hypertrophic osteo-arthritis, drugs are used symptomatically. The coal tars may be employed liberally, provided they do not interfere with digestion. It is my invariable and infrangible rule never to use cinchophen or any of its derivatives, including atophan and tolysin, for I never again want to see any patient with degenerative hepatitis, whether or not the direct relationship between the cinchophen and the hepatitis has been scientifically proven. I do not believe iodides, either in organic or inorganic form, perform any function in the dissolution of the pathologic process, though I must confess that there are patients who report that they feel better when they take iodides, even though there is no evidence of syphilis. The value of sulphanilamide remains to be demonstrated. I have never seen any of the "miracle" drugs work, whether these were of domestic origin or imported from the Continent with the usual uncritical testimony that appears without adequate data in foreign medical journals controlled by their advertisers. There is no reason that pharmacologic substances readily absorbed by mouth or rectum should be given parenterally or intravenously, other than the desire of the injector, for whatever reason, to keep the patient in constant attendance. Except for symptomatic and psychologic relief, I do not believe that the physiotherapists have a significant contribution to make, and I know that the chiropractors and osteopaths constitute a genuine menace to patients in this category—state legislatures to the contrary, notwithstanding.

As to the status of climatotherapy in atrophic arthritis, it is doubtful whether the popular wave of enthusiasm is justified by the results. In advising climatotherapy, we may be merely running away from our problem. Its good results may be either the spontaneous remission of the disease or else a purely psychologic phenomenon resulting from the escape of the patient from the tension and the strain of urban life. Many sufferers from rheumatoid

arthritis present a pathetic spectacle. Arriving sans teeth, sans tonsils, sans hope and sans pocketbook, without an adequate preliminary survey, they wander from pillar to post, usually selecting that pillar or that post where the emptiest drum makes the loudest noise. It is small wonder that so many of them, discouraged and disconsolate, as the result of their medical mismanagement, either abandon hope and accept chronic invalidism and pathetic deformity, or else seek relief in the hands of the ever-present charlatans and fakers.

Postural Strain—Faulty Body Mechanics. Postural strain and faulty body mechanics account for a huge incidence of the skeletal symptoms encountered in every-day practice. The upright position, the violation of mechanical principles in the modern vogue as to shoeing, carriage, corsetting and sitting have given rise to a vast repertory of skeletal pains as the result of the abuse of the muscles, joints, and ligaments.

The pain in acute foot strain may be sufficiently severe to simulate claudication, and the spread from this mechanical derangement may be referred to the calf, thigh, or even the lower back. As a result of the lack of orthopedic consciousness in the mind of the practitioner, these widespread disturbances are treated as vascular disease, arthritis, muscular rheumatism, and every manner of therapy introduced except the simple and curative support. Nor is it sufficient for the therapist to be content with the simple relief of symptoms. To prevent recurrence and adequately manage these strains, the cause must be sought to determine whether this is a misuse of a normal structure, an occupational strain, or a compensatory derangement as the result of a shortened leg, or a tilted pelvis, a plantar wart, a painful bunion, ill-fitting shoes, incorrect seating, the strain resulting from a long-continued application of the foot to the gasoline pedal on a long motor trip, and so forth. Where there is doubt as to the diagnosis, the therapeutic test of firm strapping, with or without manipulation, by a competent orthopedic surgeon may settle the diagnosis far better than a multiplicity of laboratory, radiographic, and specialist examinations. In peripheral vascular disease, it is almost the rule that such patients will suffer mechanical strain. Even in the presence of diminished or absent oscillometer readings and all of the clinical phenomena of impoverished circulation, therapy directed to foot mechanics may give rise to striking relief of symptoms.

In the disabilities of the lower back, resulting from postural strain, it is almost the exception to find that the patient has received adequate orthopedic care unless all other methods of therapy have been exhausted. Obstetricians and gynecologists are all too prone to the belief that lower back pain results from gynecologic abnormalities in the uterus particularly. Many patients are subjected

to a surgical procedure under this misconception. The temporary relief that follows is the result of the rest in bed rather than the operative procedure, and the symptoms recur as soon as the upright position is resumed.

Even in the presence of marked hypertrophic osteo-arthritis, adequate postural treatment and the use of corsets, both in the male and female, may give prompt relief of symptoms despite marked radiographic evidence of bony involvement. Where lower back pain exists, the first thought should be toward the correction of postural strain and the orthopedic surgeon should be the first consultant rather than to have these patients run the gamut of a medical work-up and the unnecessary ministerings of dentist, laryngologist, physiotherapist, chiropractor, osteopath, or dietitian.

The diagnosis and treatment of acute back strain, with or without radiculitis, is oftentimes woefully mismanaged in general practice. Most often the severity of the symptoms misleads the practitioner to the belief that he is dealing with a nerve lesion, colic or embolization. Therapy, for the most part, is misguided and usually consists in the overliberal use of sedatives and narcotics; when an intelligent orthopedist, by the use of manipulation, traction, and mechanical therapy, by postural treatment, the use of a Bradford frame, or a plaster jacket, may give prompt and rapid relief without the exhibition of any of the powerful analgesics. When the presence of radiculitis, particularly of sciatic distribution, accompanies postural strain or hypertrophic osteo-arthritis, the diagnostic acumen is usually further impaired and therapy even more obviously misdirected. Under these circumstances the neurologist rather than the orthopedic surgeon is consulted. The cord is investigated, spinal fluid is obtained, epidural injections practised, usually without permanent relief and certainly without effect on the underlying postural strain. The patient, battered and weary, demoralized by overdosage with sedatives and narcotics, often resorts to the chiropractor or osteopath in sheer desperation. The cause for the failure of the practitioner to recognize abnormal body mechanics most often results from his method of examination. The hospitalized patient is seen in bed and rarely made to stand so that the mechanics may be observed. In private practice the patient is usually examined stripped to the waist so that it is only by chance that the lower extremities receive even a casual examination. Even under the optimum circumstances of medical practice in the wards of our most enlightened institutions, the most exhaustive notes on charts will be found and all manner of complicated laboratory examination with little or usually no comment concerning the body mechanics.

The transition from faulty body mechanics to traumatic arthritis, peri-arthritis, fibrositis, and the phenomenon of frozen joint, is by a graduation so slight as to be imperceptible. Probably no postural

strain occurs without some organic change in the skeletal structures. By whatever name one cares to designate the condition, one meets frequently with skeletal pain, whether in the shoulder, spine, lower back, or tarsus, in which the only demonstrable physical sign is interference with function and stiffness varying from the slightest degree up to and including almost complete ankylosis. Radiographic evidences of pathologic change may be minimal or absent. The patient is often relieved rapidly and dramatically by accidental trauma or purposeful manipulation which, in the later stages, must be performed under anesthesia. This syndrome is apparently unrelated to infection or metabolic disease, and will show no therapeutic response to any form of therapy other than manipulation. Until recent times manipulation has been neglected and even completely ignored by those of us in general practice. There is no doubt but that the consciousness of the orthopedic surgeon was aroused originally by the success of the bone-setters, the early manipulators, and more recently the chiropractors and the osteopaths. This latter group have undoubtedly performed their miraculous "cures" in individuals who have been misdiagnosed and mistreated by the practitioner or internist. As the result of the failure of the latter to recognize fibrositis, either the patient himself—disgusted with legitimate medical practice—seeks the chiropractor or the osteopath or, what is even more reprehensible, the practitioner refers the patient to the manipulator or else passively consents. Those of us who are in the general practice of internal medicine must be educated to the knowledge that the modern orthopedic surgeon includes manipulation in his therapeutic armamentarium, and is more competent, if less lusty, in his management of these mechanical conditions. If the internist or practitioner chides the orthopedic surgeon concerning the introduction of manipulation into his specialty, I would suggest that he be reminded that digitalis was introduced into medicine by the investigations of William Withering into the brew of an old herbalist.

It would be amiss to leave the discussion of lower back pain without mention of the organic phenomena which may be responsible and which include spondylolisthesis, herniation of the nucleus pulposus, metastases from carcinoma, and the fascial abnormalities that have been recently stressed by Ober. From personal experience alone I am of the opinion that many patients suffer from some type of dislocation of the vertebral structures, most likely involving the articular facets. Whichever of these mechanisms is operative, this type of skeletal distress will rarely, if ever, yield to the ministerings of the dentist, laryngologist, immunologist, urologist, physiotherapist, dietitian, or drug-therapist, and a result will not be obtained until the orthopedic surgeon is consulted.

In the diseases of the peripheral vascular system the necessity for

orthopedic consultation has been stressed elsewhere. The orthopedic surgeon, should he be first consulted by these patients, must insist upon the coöperation of the internist, particularly where there exists any of the metabolic abnormalities such as diabetes, or evidence of cardiovascular renal disease.

In the varicosities involving the lower extremity, there are times when pooling of the venous blood, shunting of the arterial blood and the resulting deficient oxygenation leads to cardiac dyspnea as in arteriovenous aneurysm. If this syndrome were more particularly sought, records of observations would be more complete.

Recurrent migrating phlebitis is a baffling problem upon which internist and orthopedist collaborate. I believe that local trauma to the foot, resulting from a combination of faulty shoeing or minor contusion or abrasion, in the presence of dermatophytosis is an important etiologic factor. This is recognized in lymphangitis and lymphadenitis of the lower extremity, and this mechanism may be an equally important factor in migratory phlebitis. Whether or not this is true, the therapy in migratory phlebitis should include elimination of the dermatophytosis and careful instruction as to the care of the feet. A second important etiologic factor in migratory phlebitis is gout and the gouty diathesis. Here the therapeutic test mentioned above is the best guide. Focal infection may play a dominant rôle in the pathogenesis, not only of phlebitis, but also of endarteritis.

In clinical medicine, skeletal abnormalities may give rise to symptoms that simulate underlying visceral disease. The scalenus syndrome may suggest peripheral vascular disease or cord tumor; slipping rib, as described by Eli Moschcowitz, may resemble cholelithiasis when right sided, particularly during the last months of pregnancy, and, when left sided, the anginal syndrome. The radiculitis accompanying cervical spondylitis may give rise to precordial pain of an anginal or pleuritic nature. Albuminuria resulting from a lumbar lordosis has resulted in the anxiety and discomfort associated with the prognosis and therapy of a serious nephropathy.

Mechanical disturbances of the internal viscera may justly be included in a survey of orthopedic surgery. Gastro-visceroptosis, particularly as a manifestation of a universal ptotic habitus, may give rise to the widest variety of symptoms simulating all types of organic or glandular disturbance. When full blown the syndrome exists in angular individuals who are underweight. Such patients appear almost cachectic, the complexion is muddy, there are rings under the eyes, the blood pressure is low and the basal metabolic rate is low, contrary to expectation. All complain of asthenia, and in the women there may exist amenorrhea and sterility. These patients suggest the syndrome of pituitary cachexia or Simmonds' disease, of which this is perhaps a *forme fruste*. It is from patients

of this type that the group of individuals with rheumatoid arthritis develop. Such patients usually visit the gastro-enterologists and dieto-therapists for high calorie feedings, the endocrinologists for substitution therapy, the gynecologists for manipulative or operative treatment for retroversion, retrocession, or sterility, until, in sheer disgust, they give up completely their quest for health. The intelligent coöperation of internist and orthopedist should obtain extraordinary relief for these patients. If they will consent to prolonged institutionalization and the time-honored Weir Mitchell rest cure with corrective exercises, particularly relative to costal breathing, they may frequently gain considerable weight with complete loss of their symptoms. Pregnancy is usually associated with a great sense of well-being, but may be followed by more striking asthenia and cachexia if a prolonged postpartum rest is not prescribed.

This presentation has been devoted to a cursory and sketchy summary of the problems common to clinician and orthopedic surgeon. Many of my happiest experiences in clinical practice have resulted from this inter-relationship. Your invitation to me tonight is indicative of your understanding and willingness to cooperate with those of us who practice internal medicine. I trust that this summary may serve to interest my own colleagues more intimately in the problems dealt with so competently by the orthopedic surgeons.

THE EFFECT OF PRONTOSIL AND RELATED COMPOUNDS UPON THE CHEMOTROPISM OF LEUKOCYTES.*

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Since the adoption of prontosil and related compounds as therapeutic agents, question has arisen as to their mode of action. Other than a slight retardation of growth, Colebrook and Kenny[1] found no evidence of bactericidal activity in their work with prontosil and streptococci. Nor were they able to demonstrate any "immune response" excited by the drug. Long and Bliss[5] confirmed the results of Colebrook and Kenny in experiments *in vitro*, and from *in vivo* data were of the opinion that the results obtained in the treatment of infected mice could not be attributed entirely to a bacteriostatic action on the part of these substances. McKinney and Mellon[6] concluded that their work was opposed to the conception of a direct action of the drug on the organisms.

* This investigation was aided by a grant from the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

Since, then, it seems evident that the therapeutic action of these compounds does not depend upon the direct destruction of the organisms, other modes of activity must be supposed. The possibility of increased antibody formation might be considered, or accelerated activity of the reticulo-endothelial system, as suggested by the work of Davis, Harris and Schmeisser.[2] Another possibility that suggested itself was that these chemical agents might excite a strongly positive chemotropic response by the leukocytes and hence lead to increased phagocytic destruction of the organisms. The following experiments were undertaken to determine whether or not such an action could be demonstrated.

Method. Polymorphonuclear leukocytes were obtained by injecting physiologic saline solution into the peritoneal cavities of rabbits and withdrawing the fluid from 3 to 5 hours later. By lightly centrifugalizing this exudate and pouring off the supernatant fluid, a dense suspension of leukocytes was obtained. The cells were then suspended in plasma. The latter was procured by withdrawing 10 cc. of blood from the rabbit's heart and throwing the cells down rapidly in the centrifuge. The supernatant plasma was prevented from clotting by keeping the tubes packed in ice. A drop of the cell-plasma suspension was placed upon a coverslip and allowed to spread over a slide, upon which was the substance to be tested. In each instance this substance was placed upon the slide in the form of a tiny drop of less than 1 mm. in diameter and allowed to dry.

The directional movement of the leukocytes was then determined in relation to this drop of the test substance. The preparations were examined under the microscope at 37.5° C. and the paths of the leukocytes were charted by recording on paper their positions each minute for 10 minutes, through the use of a drawing ocular.

The measure of chemotropism adopted in these experiments was the number of micra per minute a cell moved toward, or away from, the test substance. This was computed by measuring the distance of the cell from the edge of the drop of test substance at the first and at the last observations. The difference between these two figures was divided by the number of minutes. The result was the number of microns per minute actually traversed by the cell toward, or away from, the test object. For example, if the position of a cell is 160 microns from the rim of the test object at the commencement of the observation period and 60 microns from it at the end of the 10-minute period, it has approached the substance a distance of 100 microns. This figure divided by the time (10 minutes) gives a chemotropic value of +10 microns per minute. A cell whose final position is more distant from the test substance than is its initial position has a negative value. In any experiment or group of experiments the result is expressed as the mean chemotropic value of all the leukocytes observed. The values obtained for strongly attracting substances, such as staphylococci, range from 10 to 15 microns per minute. Repelling substances give equally great negative values.

This method was used to test the chemotropic effects of prontosil, sulphanilamide and setazine.

Experiments. In the first set of experiments prontosil soluble was used. This is the 2.5% red dye solution. It is the disodium salt of 4-sulphamido-phenyl 2′-azo, 7′ acetylamino-1′ hydroxynaphthalene-3′; 6′ disulphonic acid. The preparation employed was that of Bayer ("Prontosil-Lösung, Bayer"). This solution was adsorbed

to finely powdered kaolin.* The kaolin was left in contact with the prontosil for 15 to 30 minutes. The kaolin particles were then thrown down in the centrifuge and a tiny drop of the resulting

TABLE 1.—CHEMOTROPIC EFFECT OF PRONTOSIL AND SETAZINE.

(Chemotropic effect of prontosil adsorbed on kaolin, carbon and hemolytic streptococci. No attraction of leukocytes is present. Setazine gives a slight attraction. The value in each instance is based upon 8 preparations.)

Test substances.	Mean value of chemotropism in microns per minute.
Prontosil on kaolin	−2.5
Kaolin control	−4.1
Prontosil on carbon	+0.1
Carbon control	+0.3
Prontosil on streptococci	+0.6
Streptococci control	+1.8
Setazine	+2.1

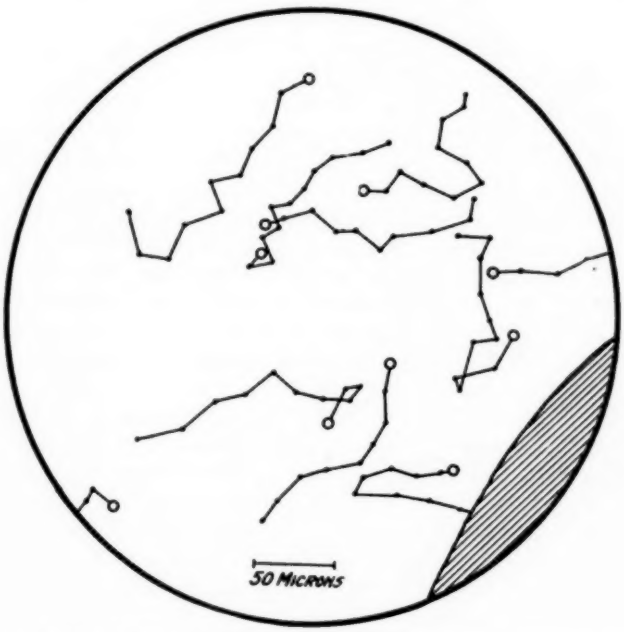

FIG. 1.—Camera lucida drawing of the paths of 10 leukocytes during a 10-minute period of observation. The shaded area represents part of a clump of hemolytic streptococci which had been treated with prontosil. The chemotropic value of this field is −0.6 micron per minute, *i. e.*, there was no attraction.

* It has previously been shown that kaolin is a satisfactory adsorbing agent for chemotropic substances.[3,7]

heavy suspension was placed upon a slide and allowed to dry. The kaolin was stained pink by the prontosil and after the preparations were made, the dye was seen to diffuse slowly into the surrounding medium. A control drop of kaolin in double-distilled water was made upon the same slide a few millimeters away.

In 8 experiments with kaolin plus prontosil the mean value of chemotropism was −2.5 micra per minute based on 191 cells. In the control fields containing kaolin alone, the value was −4.1 micra per minute for 105 cells. The prontosil, then, had apparently slightly decreased the negative chemotropism of kaolin, by 1.6 micra per minute. To determine whether or not the difference between the control and test figures was significant the standard error was computed for each set of figures. The mean and standard error based on the 191 cells of the kaolin-prontosil fields is -2.5 ± 0.36. The mean and standard error based on the 105 cells of the kaolin control fields is -4.1 ± 0.57. The difference with its standard error is 1.6 ± 0.67. Consequently there is a real difference between kaolin prontosil and the kaolin control, since the difference is more than twice its standard error; equal or greater differences would occur by chance only twice in 100 times.[4] Hence prontosil, though it did not bring about positive chemotropism, did slightly decrease the negative chemotropic effect of kaolin.

Similar experiments were conducted with carbon particles as the adsorbing agent for the prontosil solution, using untreated carbon as the control. Eighty-two cells were examined in the carbon-prontosil fields and 76 cells in the carbon control fields. The cells in the carbon-prontosil fields gave a chemotropic value of 0.1 micron per minute toward the test substance. The control series gave a figure of 0.3 micron per minute toward the carbon. In other words, both control and test substances showed essentially indifferent movement of the cells. The standard errors were 0.53 and 0.71 respectively, and the difference between test and control values was found to be insignificant.

Though prontosil did not attract leukocytes, yet it seemed not unlikely that it would increase the chemotropic effect of streptococci when these were treated with the dye. Therefore in the next set of experiments, a strain of hemolytic streptococci, No. 1048, was employed. Preparations were made consisting of the streptococci from broth cultures, washed several times in double-distilled water. These organisms were allowed to remain in the 2.5% prontosil solution for periods varying from ½ hour to overnight, after which they were washed once and then placed on the slide. The control on the same slide consisted of washed, but otherwise untreated, streptococci. The results are based on 8 experiments and a total of 97 leukocytes in the microscopic fields containing streptococci treated with prontosil, and 98 leukocytes in the control fields. The cells in the streptococci-prontosil fields showed a positive chemo-

tropic value of 0.6 micron per minute. The control cells moved 1.8 micron per minute toward the untreated streptococci. The standard errors were 0.68 and 0.52 respectively, and the difference between these figures was found to be insignificant by application of the statistical method referred to above.

In another group of experiments, preparations were made with sulphanilamide (Merck). Sulphanilamide is para-amino-benzene-sulphonamide. Crystals of this substance in double-distilled water were employed. In every instance, the leukocytes were apparently paralyzed by the concentration of the drug used. The cells failed to move in the neighborhood of the sulphanilamide crystals and would often appear to float in the plasma, suggesting a possible liquefaction of the plasma gel.

Similar preparations were made using setazine crystals. Setazine is the benzoyl derivative of sulphanilamide (Merck). Two hundred and seventy-six cells were followed in 8 preparations. It was found that the cells were attracted toward the setazine at a rate of 2.08 microns per minute. The standard error was 0.18. When compared to a mean of zero, the figure for setazine is significant, although in several of the preparations there was no attraction.

Summary. Experiments have been conducted using prontosil adsorbed on kaolin, carbon and streptococci in an attempt to determine the chemotropic effect of the drug for polymorphonuclear leukocytes. Leukocytes were obtained from the peritoneal cavity of the rabbit. Although the prontosil slightly reduced the negatively chemotropic effect of kaolin, it did not cause a positive chemotropic response. Adsorbed to carbon and to streptococci the prontosil did not alter the directional movement of the leukocytes in relation to the adsorbing agents. There is, then, no evidence from these experiments that prontosil attracts leukocytes.

Experiments in which sulphanilamide was used as the attracting substance showed that this substance, in the concentrations used, exerted a toxic effect upon the leukocytes which was expressed in a cessation of their movements.

Experiments using setazine as the source of attraction showed that this substance exerted only a weak attraction for the leukocytes and this was not constant.

It seems unlikely from these experiments that the therapeutic action of these drugs is due to an increased chemotropism of polymorphonuclear leukocytes.

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BOOK REVIEWS AND NOTICES.

A METHOD OF ANATOMY. Descriptive and Deductive. By J. C. BOILEAU GRANT, M.C., M.B., CH.B., F.R.C.S. (EDIN.), Professor of Anatomy in the University of Toronto. Pp. 650; 564 illustrations. Baltimore: William Wood & Co., 1937. Price, $6.00.

UNDER the above title the author has produced a book on human anatomy designed chiefly for use by the medical or dental student in connection with dissection. The structures of the human body are described by regions rather than by systems and there are sporadic directions for the dissection of certain structures.

In his preface Grant states that his purpose is to present human anatomy in such a way that the student, by learning to correlate facts by studying them in their mutual relationships, will be led "inevitably to the apprehending of the underlying principles involved and the 'raison d'être' of such relationships. The student will thus learn to reason anatomically . . . ." And again he says: "The book is meant to be a working instrument designed to make Anatomy rational, interesting and of direct application to the problems of medicine and surgery."

Thus, instead of a conventional, systematic description, a running account of each region is given, in which he brings out rather strikingly, and with the aid of simple line drawings and explanatory diagrams (some of which are of the nature of animated cartoons), the principal features of the region, always attempting to correlate structure with function; and adding salient embryologic data, and brief clinical applications. Perhaps the most successful contributions consist in the bringing of ligaments to life, and in the interesting treatment of the joints, particularly of the hand and foot.

Following the lead of the latest edition of Cunningham, the nomenclature as revived by the British Anatomical Association (B.R.) is used. With Toldt's Atlas employing a special German Revision (N.K.) while all others except the British writers adhere to the internationally adopted B.N.A., the terminology appears to be reverting to chaos. Since there is a new international committee at work on a revision of the B.N.A. this outcropping of nationalistic nomenclature rebellion seems regrettable.

Just what place the book will find is difficult to predict. It is not complete enough to replace, for medical students, the systematic textbooks and atlases and is rather too extensive to be used generally as an addition to them. Possibly its most important mission will be to stimulate the established textbooks of anatomy to adopt a more functional standpoint, and to introduce more analytical and explanatory diagrams. It is a readable account of anatomy, and it brings out many anatomic facts in such an interesting and striking way that they seem to assume a new significance.

E. C.

MANUAL OF CLINICAL AND LABORATORY TECHNIC. By HIRAM B. WEISS, A.B., M.D., F.A.C.P., Associate Professor of Medicine, College of Medicine, University of Cincinnati, and RAPHAEL ISAACS, A.M., M.D., F.A.C.P., Associate Professor of Medicine; Assistant Director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan. Pp. 141. Philadelphia: W. B. Saunders Company, 1937. Price, $1.50.

THE fifth edition of this manual has been revised to include several of the newer diagnostic procedures, especially in hematologic technique. The

volume compares favorably with similar technique manuals issued by the larger hospitals for their interns. It shares their advantages of covering much territory in a small compass and their disadvantages of being incomplete both as to subject matter and details of technique and interpretation. It includes, as formerly, sections on history taking and routine physical examination, on clinical laboratory technique, on technical ward procedures and tables of nutrition values. No attempt is made to cover the bacteriologic, serologic or chemical laboratory technique except for such procedures as might be carried out in an office practice. J. F.

Le Traitement de la Tuberculose Pulmonaire par la Tuberculine. By Dr. M. Jaquerod (Leysin). Pp. 43; 2 plates. Lausanne: Librarie Payot & Cie., 1937. Price, 2.50 Sw. fr.

The author concludes from extensive clinical experience that tuberculin treatment, in properly selected patients, is an effective supplement to rest therapy and collapse measures. Repeated warning is given against the indiscriminate application of tuberculin. It should be rigidly restricted to the patient with chronic afebrile, torpid disease. However, about a quarter of all cases of tuberculosis are considered suitable. No extravagant claims are made, and the author's discussion is persuasive, although no experimental or statistical evidence is presented. The details of treatment are described in simple fashion in this volume.

H. I.

Artificial Fever. Produced by Physical Means; Its Development and Application. By Clarence A. Neymann, A.B., M.D., F.R.S.M., Associate Professor of Psychiatry, Northwestern University Medical School; Honorary Professor of Medicine, National University of Mexico, etc. Pp. 294; 68 illustrations and 21 tables. Springfield, Ill.: Charles C Thomas, 1937. Price, $6.00.

During the past 10 years much work has been done on artificial fever produced by physical means. Dr. Neymann has compiled the results of this research in an interestingly written and welcome book. Important statements are italicized or printed in heavy type. The paper, printing, illustrations, charts and binding are very good. There are several minor typographical errors. The price is high for 300 pages.

The first 2 of the 15 chapters deal with basic theories, principles and the history of hyperpyrexia. The author points out that the production of artificial fever was not a haphazard affair, as several lay articles would have us believe, but was the result of the carefully thought-out researches of Neymann and Osborne. This fact is mentioned no less than six times in the first 100 pages.

The next 3 chapters deal with the physiology and technique of hyperpyrexia. Here the emphasis on rectal temperature control of the patient and many treatment details are valuable. Neymann is convinced that his method (electromagnetic induction) is the best, and he offers arguments for it and against the other means of producing fever. The book could be improved by a more complete and unbiased discussion of air-conditioned and infra-red cabinets.

The remainder of the book considers the treatment of individual diseases with artificial fever therapy. Separate chapters are allotted to Paresis, Tabes and Cerebrospinal Syphilis, Primary and Secondary Syphilis, Multiple Sclerosis, Chorea Minor, Arthritis, Gonorrhea, and Asthma. Each chapter contains brief historic and clinical discussions of the disease which

have a doubtful place and value. The technique for each condition is covered especially as to the range of temperature, duration and number of treatments. The author states clearly what may be expected of fever therapy. When other therapy is indicated, as in syphilis, Dr. Neymann strongly recommends it, but at times with insufficient detail. He frankly rates pyrexia as ineffective alone in early syphilis, a commendable conservatism. The chapter on gonorrhea is well written in spite of the author's limited experience of only 3 cases.

Throughout the work, a discursive and conversational style, anecdotal technique in case description, a disposition to generalize, often sweepingly on an experience or two and occasional loose statements about results, detract from the value of the work as a scientific contribution. Nonetheless overenthusiasm is avoided to the extent that non-fever methods get emphatic endorsement whenever applicable.

There is an excellent bibliography of 556 references. This book should be read by all physicians and technicians doing fever therapy work. It will give the general practitioner a survey of the indications, results to be expected and the limitations of hyperpyrexia, but he should not expect an unbiased discussion of the means of producing fever. J. F.

HEART DISEASE IN GENERAL PRACTICE. By PAUL D. WHITE, A.B., M.D., Assistant Professor of Medicine, Harvard University Medical School. Edited by MORRIS FISHBEIN, M.D. Pp. 338; 45 figures. New York: National Medical Book Company, Inc., 1937.

IN his preface the author states that he has compiled "a brief but practical and forceful summary of our present knowledge of the diagnosis, prognosis, and treatment of heart disease." The type of presentation throughout the main part of the book is that of questions and answers. In all, 152 questions are asked and answered. Sample questions are as follows: Is "indigestion" caused by heart disease? Of what value is blood pressure determination? Of what relative value are the so-called laboratory methods in cardiovascular examination? (the answer of this is given in percentage figures). May the "cardiac" child go to school?

In addition to the main part of the book, there is an appendix of 43 pages devoted to the proper handling of cardiovascular emergencies or "heart attacks."

There is undoubtedly a great need for books of this type, not only on heart disease but in practically every field of clinical medicine. The author is preëminently fitted for his task, not only by virtue of his comprehensive and accurate knowledge of the subject and his ability as a writer, but also his experience in giving courses for physicians. The less a practitioner who has to deal with heart disease knows about it, the more he needs this book. After he has learned the answers to the 152 questions, he will at least have a good start. C. W.

BIOLOGICAL AND CLINICAL CHEMISTRY. By MATTHEW STEEL, PH.D., Professor of Biochemistry in the Long Island College of Medicine, Brooklyn, N. Y. Pp. 770; 21 illustrations and 58 tables. Philadelphia: Lea & Febiger, 1937. Price, $8.00.

IN this book "the author has attempted to blend theoretical and practical biochemistry and biophysics with chemical pathology and clinico-chemical methods." The student is taught to use himself as a clinical subject, and perform on himself the many tests that are used in the modern study of the patient. Emphasis is laid upon the chemical separations that accompany

pathologic processes, rather than upon general biochemistry. A large number of experiments are detailed to illustrate the subject matter of the text. The book is readable and no doubt fulfills the purpose for which it is intended. B. L.

JOURNAL OF NEUROPHYSIOLOGY (Issued Bi-monthly), Vol. I, No. 1, January, 1938. Editorial Board: J. G. DUSSER DE BARENNE (Yale), J. F. FULTON (Yale), R. W. GERARD (Chicago), with an Advisory Board of 25. Pp. 85; illustrated. Springfield, Ill.: Charles C Thomas, 1938. Price, $6.00 per volume.

THE first issue of this new journal contains 9 articles, 3 of which deal with peripheral nerve, 6 with cerebral cortex. They are concisely written and of enough importance to challenge the attention of readers following this field. It is only occasionally that a paper appears which fixes a conclusion in the memory with a clarity and force that promises permanence. The present Reviewer confesses that for him such experiences are rare; yet he has met two in this single issue: "Forced Circling Movements in Monkeys Following Lesions of the Frontal Lobes," by M. A. Kennard and L. Ectors, and "Functional Organization in the Sensory Cortex of the Monkey," by J. G. Dusser de Bareene and W. S. McCulloch. The first number of this new journal justifies the editors in its inception and augurs well for its future. G. McC.

CLAUDE BERNARD, PHYSIOLOGIST. By J. M. D. OLMSTED, Professor of Physiology, University of California. Pp. 272; illustrated. New York: Harper & Brothers, 1938. Price, $4.00.

Claude Bernard, unquestionably one of the greatest pioneers in 19th century medical progress—Carrel's Foreword calls him "the father of modern medicine"—has received far less biographic attention in English than has his great contemporary and friend, Pasteur. Sir Michael Foster's out-of-print and not altogether sympathetic volume is, according to the author, the only book-length treatment of Bernard's life that exists in English, and even the French sources appear to be none too detailed or accurate. This volume, then, fills a conspicuous want and is especially welcome when written by an eminent physiologist whose interest of long standing has of recent years blossomed into painstaking, constructive first-hand study of the master physiologist. Many may not agree with him that "on a sufficiently broad view, Claude Bernard towers above Pasteur today as he did during his lifetime;" yet as one who more than any one else substituted the scientific method for empiricism in medicine, his importance is indeed incalculable. His enviable scientific method, and his emphasis on the value of experimentation are of almost equal importance. His concept of the "*milieu intérieure*" has only recently attained recognition as one of the most important basic principles of animal physiology; and his studies of pancreas and liver function properly place him as the father of modern endocrinology.

Like all great men, he had, of course, his weaknesses and made his mistakes. Possessing an ardent loyal personality, he was led by his master's (Magendie) incorrect observations of the complete absence of circulation in some cholera cases to a false theory of the lack of indispensability of the blood; his intense nationalism led him to claim for Frenchmen, including himself, discoveries that others attributed to English and German scientists; his numerous books, mostly from students' transcripts of his lectures, thereby necessarily contain repetitions, contradictions and inaccuracies. Curiously, his first book to be published from his lectures was in English, prepared by Walter F. Atlee, a young Philadelphia physician.

As well as making an excellent critical study of the great scientist, his methods and professional achievements, the author gives a lively picture of the man, his triumphs and his misfortunes, his foibles and his lovable qualities. Here the copious Raffalovich correspondence has been used to good effect. Next to Bernard's own unfinished "Introduction to the Study of Experimental Medicine," one can recommend the study of this volume as a means of getting to know more about one of the greatest figures in the history of modern medicine. E. K.

PRACTICAL BACTERIOLOGY, HÆMATOLOGY, AND ANIMAL PARASITOLOGY. By E. R. STITT, M.D., Sc.D., LL.D., Rear Admiral, Medical Corps, and Surgeon General, United States Navy, Retired; formerly Associate Professor of Medical Zoölogy, University of the Philippines; PAUL W. CLOUGH, M.D., Chief of Diagnostic Clinic, Johns Hopkins Hospital; Associate in Medicine, Johns Hopkins University, etc.; and MILDRED C. CLOUGH, M.D., formerly Fellow in Bacteriology and Instructor in Medicine, Johns Hopkins University. Pp. 961; 208 illustrations (4 in colors). Ninth edition, rewritten, revised and enlarged. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $7.00.

THE ninth edition of this well-known book is prepared in the usual excellent fashion. As compared to the eighth edition, the text is increased by 124 pages and all material gives evidence of extensive revision and rearrangement. Chapters on Rickettsia and Bartonella and on filterable viruses have been added to Part I, Bacteriology, and discussion of Spirochetes transferred to this section. To Part II, Hematology (Study of Blood, eighth edition), expanded from 67 to 95 pages, has been added 2 colored plates and 2 colored drawings from cases of leukemia and a chapter on Diseases of the Blood. Illustrations for the section on Animal Parasites, Part III, are improved. Part IV, Pathological Examination of various Fluid and Organs, is more than doubled in size. Chapters on Examination of Blood and Urine, and on Liver and Kidney Function have been included here rather than in the Appendix, and 2 new chapters, Endocrine Glands and Food Deficiency Disease, added. The authors and publishers are to be congratulated. H. R.

DAS RHEUMABUCH DES DOCTOR BALLONIUS. Nach der Rheumaschrift des Lateinischen Textes. Gulielmi Ballonii, Liber de Rheumatismo et Pleuritide Dorsali, Paris, 1642. Deutsch Herausgegeben VON DR. WALTER RUHMANN, Specialarzt für Innere Krankheiten in Berlin. Pp. 66. 1 illustration. Mittenwald: Arthur Nemayer, 1938. Price, Rm. 3.

THIS booklet, from a Press that seems to specialize on rheumatism, is chiefly concerned with rendering Guillaume de Baillou's book on rheumatism "aus der starren lateinischen Form in unser lebendiges Deutsch!" Doubtless for Germans the translated text is both more alive and clearer than to those for whom it is still in a foreign language. A short Anhang compares old and new rheumatism in an unenlightening manner: toxins, hormones and antibodies are correlated with the ancient doctrine of the humors, "shifts to the lift" and "allergizing factors" hover about the effort to interpret the language of ancient medicine in terms of the combination of a new humoral pathology with Virchow's Cellular Pathology. To the author, for whom the study and treatment of disease are in a state of flux, Ballonius' work serves as an example of old knowledge attaining to new truths, though the Reviewer must confess that he cannot follow the sequence. E. K.

THEORETICAL PRINCIPLES OF ROENTGEN THERAPY. Edited by ERNST A. POHLE, M.D., PH.D., F.A.C.R., Professor of Radiology; Chairman, Department of Radiology and Physical Therapy, University of Wisconsin. Foreword by W. EDWARD CHAMBERLAIN, B.S., M.D., F.A.C.R., Professor of Radiology in the Temple University School of Medicine, Philadelphia. Pp. 271; 132 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $4.50.

THIS book presents the fundamental facts concerning Roentgen therapy in such a manner as may be easily assimilated by students of radiology even though they may not have a complete knowledge of physics. The entire book is compiled in such a way that one paragraph builds up the subject matter for subsequent paragraphs. The physical properties of the book such as the print and paper are of excellent quality.

The book deserves a place in every radiologic department. Any criticisms which are made of this text are minor. Since the book is a compilation of the work of different men, there is some tendency to overlap the subject matter. This does not detract from the quality of the book but rather aids in presenting more than one man's opinion of the same subject.

The chapters on dosimetry and protection from Roentgen ray are unusually practical and in themselves comprise a real asset to the library of any radiologist. G. C.

THE PATIENT AND THE WEATHER. By WILLIAM F. PETERSEN, M.D. With the assistance of MARGARET E. MILLIKEN, S.M. Volume IV, Part 3, Organic Disease Surgical Problems. Pp. 651 (lithoprinted); 482 illustrations. Ann Arbor: Edwards Brothers, Inc., 1938. Price, $10.00.

REGRET is expressed that the important work in this realm by investigators in continental Europe is comparatively unknown to English and American writers. This volume, the last but one of the series, is divided into 14 chapters, and the major subjects discussed are as follows: Infections and inflammation; ulcer of the stomach and duodenum, and Meckel's diverticulum; meteorologic environment and the gall-bladder attack; appendicitis; disturbances of the bowel; ectopic pregnancy; postoperative complications; vascular accidents; miscellaneous episodes; brain abscess; orthopedic cases; ophthalmologic episodes; glaucoma; endemiology of the surgical cases; concluding chapter being a brief résumé.

The chapter on infection and inflammation is given most space, wherein the weather is stated to be a dominating factor in initiating the two major biologic rhythms—ARS and COD—and by their observance, the surgeon will be greatly aided. ARS phase shows anabolism and alkalosis, with increased blood pressure; there are reductive processes and contraction of smooth muscle fibers; hemorrhage and embolism are more apt to occur; spasm of sphincters and increased tension of scars; adhesions may tear and hollow viscera rupture; focal lesions become painful; drains may be expelled, sutures give way and herniotomy may occur(?). COD phase follows, with dilatation of arterioles, capillaries and venules, and blood pressure falls; oxidation and catabolism are enhanced; thrombosis and venous bleeding may occur; tissues swell, tension is increased and greater pain is experienced; muscle spasm and connective tissue spasm relax and healing is accelerated; temperature, pulse rate and metabolism are increased. Since many minor rhythms make up the major ones, the dividing line is not so sharp as the description may suggest.

With this volume, the study of the effect of environment upon organic disease is concluded. In the next, and final volume, "conception, morbidity, death and the relation of these to evolution," will be considered in a

more abstract form. This ponderous series, devoted to a much neglected subject, cannot be read lightly. The Reviewer again expresses the hope that the reader may be aided by the addition of an index to the concluding volume. N. Y.

THE BIOLOGY OF ARTERIOSCLEROSIS. By M. C. WINTERNITZ, M.D., R.M. THOMAS, M.D., and P. M. LECOMPTE, M.D., The Department of Pathology, Yale University School of Medicine, New Haven. Pp. 142; 116 illustrations (many in color). Springfield, Ill.: Charles C Thomas, 1938. Price, $4.00.

THOUGH diseases of the cardiovascular system head the causes of death, knowledge concerning their nature is still very incomplete. The causes of arteriosclerosis remain unknown, and the steps that lead to the development of the full-bloom state are obscure. The present monograph deals primarily with the interpretation of the structural changes in the diseased vessel wall; it represents an attempt to trace the processes to the inception and to follow them through their various stages. From this study there emerges a unified concept as to the nature of the sclerotic processes in the arteries, in the heart valves and in the veins.

In an age in which the latest method is often looked upon as the best, it is worthy of emphasis that the authors have made use of old tools and done so with striking success. They have employed clearing agents to render transparent whole vessel, and injection fluids to bring into view the vasa vasorum, and they have carefully dissected the cleared and injected vessels, coat by coat. By these means, now so greatly neglected, they were able to establish a better correlation between structures and lesions visible to the naked eye, and the subvisible; moreover preliminary study of the cleared and injected vessel has enabled them to select with ease and precision areas of particular interest for more detailed histologic investigation. One of the outstanding results of their study is the demonstration that an extensive vascular network of regular pattern ramifies throughout all the coats of the vessel wall. In response to various stimuli much proliferation of these vasa vasorum may take place, and some may attain considerable size. In the diseased artery, mural vascularity becomes greatly exaggerated.

The recognition that the walls of blood-vessels are richly vascular, forms the point of departure in the present investigation. The authors proceed to study the reactions of the vessel wall to injurious agents. They show that here, as in all other vascular tissue, exudation and proliferation occur as consequence of many types of injury, and that these reactions play a dominant part in the complex picture of arteriosclerosis. Of particular importance is hemorrhage from the vasa vasorum, for it may become very extensive, and lead to sudden occlusion of the lumen by rapid infiltration of the wall; or the leakage may be slow and less extensive and bring into activity processes that lead to removal of the escaped blood or to its organization, and to repair of the damaged wall. These are events of common occurrence and they, too, enter into the picture of the sclerotic processes. Intimately related to arteriosclerosis proper, is the mechanism of calcification, of atheromatous formation and of thrombosis, and these subjects are considered in the light of disturbed mural vascularity.

The authors did not find the causes of arteriosclerosis, nor did they furnish the solution of many of the multitudinous questions that arise when this disease is critically discussed. But they have added much of value to our knowledge, and their work marks a long forward step toward placing the problems of arteriosclerosis on a sounder basis. This monograph makes very stimulating reading, and clarifies the current, hazy, and ill-founded conceptions concerning arteriosclerosis.

Not the least valuable part of this thought-provoking book is the wealth of beautiful illustrations, many of their reproductions of photographs taken in natural colors. But a few years since, illustrations such as these would have placed the book beyond the pocket-book of most of us. At long last we have an American medical publication with an abundance of truly excellent colored illustrations published at a very moderate price.

B. L.

THE NEW INTERNATIONAL CLINICS. Vol. 1, New Series (Old 48), March, 1938. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 18 Collaborators. Pp. 322; illustrated. Philadelphia: J. B. Lippincott Co., 1938.

A NEW series of this distinguished periodical, now in its 189th volume, starts with this issue in a different and more attractive cover. Dr. Piersol's experienced leadership should go far in making the "Clinics" succeed, and all the more with the following distinguished list of American and foreign collaborators: F. G. Blake, R. L. Cecil, V. C. David, N. J. Eastman, K. M. Houser, W. J. Kerr, J. W. McNee, J. C. Meakins, G. R. Minot, J. W. Moore, J. H. Musser, L. J. Pollock, I. S. Ravdin, E. Rehn, B. S. Veeder, B. G. Wallace, R. M. Wilder, and A. C. Woods. International medicine, surgery, obstetrics and gynecology, pediatrics, neuro-psychiatry, ophthalmology, otolaryngology, and pharmacology are thus all represented by leaders of their specialties.

This number consists of 17 original contributions, 8 "clinics," and a review of recent contributions to biliary stasis and decompression, by A. Cantarow.

E. K.

THE TREATMENT OF CLINICAL AND LABORATORY DATA. An Introduction to Statistical Ideas and Methods for Medical and Dental Workers. By DONALD MAINLAND, M.B., CH.B., D.SC. (EDIN.), Professor of Anatomy, Dalhousie University, Halifax, Nova Scotia. Pp. 340; 23 illustrations. London: Oliver and Boyd, 1938. Price, 15/-.

THIS book on statistical methods has several advantages over other works on the subject. These advantages are that it can be understood by every physician, it is actually readable and interesting, the problems may be worked by any one having a knowledge of arithmetic and elementary algebra, and most noteworthy, the examples are familiar to everyone practicing medicine. Thus the reader is shown exactly how to answer such questions as these: When is an increase from 70 to 80% of polymorphonuclears in a differential count significant, and when is it due to chance? To what extent are large samples of observations more reliable than small samples, and how large should samples be? What is the probability that two small series of blood pressure readings are significantly different? These are problems that nearly everyone meets, and consequently this book should be useful to a great many readers, especially to those who know nothing about statistical methods and perhaps distrust them.

The Reviewer suggests that when a second edition is brought out, it should include a few tables, so that it would not be necessary to refer the reader so often to other books containing tables. An example of how this may be done is given in Appendix III of H. L. Dunn's paper on "Statistical Methods in Physiology" (*Physiol. Rev.*, **9**, 275, 1929); these tables may be profitably used by readers of Dr. Mainland's book.

M. McC.

ON THOUGHT IN MEDICINE (DAS DENKEN IN DER MEDIZIN). By HERMANN VON HELMHOLTZ. An address delivered August 2, 1877, on the Anniversary of the Foundation of the Institute for the Education of Army Surgeons. Introduction by ARNO B. LUCKHARDT. (Reprinted from Bulletin of the Institute of the History of Medicine, Vol. 6, No. 2, February, 1938). Pp. 27; 2 illustrations. Baltimore: The Johns Hopkins Press, 1938. Price, .75.

THIS reprint, consisting of a translation of Helmholtz' celebrated address, delivered in 1877 on the Anniversary of the Foundation of the Institute for the Education of Army Surgeons and a 3-page introduction by Arno B. Luckhardt, is a welcome addition to the output of the Hopkins Institute. Not a little of Helmholtz' address is as appropriate today as it was 60 years ago and probably will be 60 years from now. Perhaps we should be content that in some parts of the world *some* progress has been made in substituting observation, experiment and fact for theory and metaphysics.

E. K.

ON A NEW GLAND IN MAN AND SEVERAL MAMMALS (GLANDULÆ PARATHYREOIDEÆ). By IVAR SANDSTRÖM. [Upsala Läkareförenings Förhandlingar, 1879–80, **15**, 441–471]. Translated by CARL M. SEIPEL, DR. MED. DENT. Edited by CHARLOTTE H. PETERS and J. F. FULTON. With biographical notes by PROF. J. AUGUST HAMMAR. Pp. 44; 1 illustration and 3 plates. Baltimore: The Johns Hopkins Press, 1938. Price, $1.00.

THIS English translation is the only complete translation from the Swedish of the 30-page article by Sandström in 1880 which first described the parathyroid glands, which he had discovered when he was still a medical student. This is preceded by an interesting brief note on Sandström's life written by Hammar, an English abstract of Hammar's review on the parathyroids written in Swedish in 1908, and a translation of a letter from Sandström to his sister, which reveals his idealism in research. This is an attractive little book for those interested in looking back upon the important and dramatic steps in the development of medical knowledge.

I. Z.

ATHLETIC INJURIES. Prevention, Diagnosis and Treatment. By AUGUSTUS THORNDIKE, JR., M.D., Surgeon in the Department of Hygiene, Harvard University; Assistant in Surgery, Harvard Medical School, etc. Pp. 208; 104 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $3.00.

A MONOGRAPH of importance. Any school physician will benefit by reading the chapters on "Physical Fitness, "Physician Training," and "Physical Fatigue." The remainder of the book is a concise and valuable treatise upon the diagnosis and treatment of injuries sustained in sports.

G. W.

PNEUMONIA AND SERUM THERAPY. By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc., and RODERICK HEFFRON, M.D., Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health, 1931–1935. Pp. 148; 10 figures and 10 tables. Revised edition of Lobar Pneumonia and Serum Therapy. New York: The Commonwealth Fund, 1938. Price, $1.00.

THIS small volume is a revision of one published in 1936 under the title of "Lobar Pneumonia and Serum Therapy." Detailed information is included concerning the administration of the newer antipneumococcus

sera, both horse and rabbit. Reference is made to the results now beginning to appear from some of the State pneumonia control programs. To the general practitioner as well as the reader of more limited interests this little book should prove extremely useful. L. C.

HERNIA. Anatomy, Etiology, Symptoms, Diagnosis, Differential Diagnosis, Prognosis, and the Operative and Injection Treatment. By LEIGH F. WATSON, M.D., Member of Attending Staff of California Lutheran Hospital and Methodist Hospital of Southern California, Los Angeles. Pp. 591; 281 illustrations. Second Edition. St. Louis: The C. V. Mosby Co., 1938. Price, $7.50.

THIS second edition adds much of value for the reader. It, as does the first edition, presents the necessary features of anatomy, etiology, symptoms, signs, diagnosis, prognosis and mortality factors in the consideration of the care and treatment of this very common and important surgical condition.

The historic sketches are well done and extremely interesting, being more condensed and concise than in the first edition; also many of the older types of operations, proven impractical, have been omitted. Still too many are included for practical usage. The chapters on the medico-legal and compensation aspects of hernia have been thoroughly scrutinized and brought up to date. Several excellent chapters on the popular injection treatment are added. Comparisons between this and the operative treatment are made as to the complications, recurrences, expense, discomfort, mortality and time elements concerned.

The illustrations are very good on the whole and but few examples of monstrosities, instruments and the author's "pets" are included—a pleasing innovation. The new illustrations concerning the injection treatment are especially well done and useful.

The bibliography is very extensive, up to date and thorough, making this a real reference work.

There are, however, some minor adverse criticisms that must be noted. For example, the use of strychnia and such drugs for shock, mercurochrome for skin antisepsis, a different preoperative and postoperative skin preparation, inappropriate amount of space given to operative room technique—care of needles, sutures, dressings, etc. Added to these is the use of cocaine for local use, the objection to spinal anesthesia in the diabetic and the operative emptying of the proximal distended loop of gut in obstructed cases, on the basis of toxicity, this being responsible for reducing the mortality 25 to 50%.

Local anesthesia does not unfortunately answer the whole question of postoperative pulmonary complications as one infers from the author's statements.

With the exception of these few minor points the book is a very excellent one, well written, thorough, interesting, instructive and a valuable addition to any surgeon's library. E. E.

DIGESTIVE TRACT PAIN. Diagnosis and Treatment. Experimental Observations. By CHESTER M. JONES, M.D., Assistant Professor of Medicine, Harvard University; Physician, Massachusetts General Hospital. Pp. 152; 5 figures and 1 plate. New York: The Macmillan Company, 1938. Price, $2.50.

THE author states "It is the purpose of this little book to present a study on pain and other similar sensations caused by disturbances of the digestive tract." Admittedly abdominal pain is the major symptom upon which the clinician must depend for the accurate diagnosis of gastro-intestinal disease. The work is based upon both experimental data and clinical observations.

There are 8 chapters, a short bibliography and a very satisfactory index. The relation of the work of Ross, and Mackenzie and Head, to the observations of more recent investigators is discussed in a delightful introduction. There follows a most interesting chapter on "Heartburn." In regard to this symptom the author states "that these symptoms may be associated with actual regurgitation of stomach contents, which at times reach the mouth, is not to be doubted, but that the character of the regurgitated fluid has much, if anything, to do with the cause of the symptom is open to very grave doubts. There then follows in sequence a description of the reference of pain from the entire gastro-intestinal tract after which is a chapter on the "Clinical Application of the Experimental Observations." Many clinical protocols are included in the remaining portion of the volume. These in fact take up more than one-half of the volume. A unique feature is the chapter on "Gastro-intestinal Pain in Functional Disease." Every practitioner of experience realizes the necessity of considering the psychogenic aspects of patients with functional disease. This little volume is simply and well written so that it makes easy reading. It is a worthy addition to the Macmillan Medical Monographs. I. R.

SOME ACCOUNT OF THE PENNSYLVANIA HOSPITAL. From its First Rise to the Beginning of the Year 1938. By FRANCIS R. PACKARD, M.D. Pp. 133; illustrated. Philadelphia: Printed by the Engle Press for the Pennsylvania Hospital, 1938. Price, $2.50. (Books are obtainable from the Pennsylvania Hospital, 8th and Spruce Sts., Philadelphia.)

THE Pennsylvania Hospital, in its long history as the oldest independent hospital for the care of the sick in this country, has been singularly fortunate in its historians. Following Benjamin Franklin's "Some Account," printed by him in 1754, we have Malin's short account in 1831, George B. Wood's history of the first century (1851), J. Forsyth Meigs' history of the next 25 years (1876) and Thomas G. Morton's extremely detailed account of 1895. Its very completeness, however, militates against the readability of Morton's history, so that lovers of the Hospital would now for some years have welcomed a brief account that would again bring its history up to date in pleasant form for the general reader. For this task none could have been better fitted than the present author—a medical historian of note, with a charming style, and long steeped in the traditions of the Hospital that he has served so long and well. He certainly has achieved his purpose of presenting "in as nearly as possible narrative form a brief account of the chief points of interest" of the institution.

Beginning with a brief account of the hospital's memorable foundation, the narrative recalls to us the colonial atmosphere of its early years, the early buildings, Franklin's incomparable cornerstone inscription, early expedients for raising money, the "elaboratory," the sunstroke tent and similar vivid pictures. Medical teaching, the Pathological Museum and Laboratory, the Out Patient Department, the Training School for Nurses, the Department for Mental and Nervous Diseases, and the Pennsylvania Hospital Unit in the World War, all have their high points of interest presented. There is no index, nor is one to be desired in a narrative that does not aim at reference use. The list of official prints of the Hospital, however, is an innovation of distinct reference value.

The typography (Caslon) and format of Franklin's "Account" has been copied to good effect. The illustrations, which are well chosen and reproduced, constitute an especially pleasant feature for those acquainted with the Hospital: rare portraits of the first staff, some of the Fothergill plates, hospital views, pleasant little drawings of hospital nooks and memorabilia by F. deP. Rothermal and photographs by E. F. Forney, all add to the attractiveness of a book that will be prized by the Hospital's many friends and appreciated by an even wider circle. E. K.

NEW BOOKS.

Practical Otology, Rhinology, and Laryngology. By ADAM EDWARD SCHLANSER, M.D., Colonel, Medical Corps, United States Army; Chief of the Eye, Ear, Nose and Throat Service, Letterman General Hospital, San Francisco, etc. Pp. 315; 81 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $4.50.

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PROGRESS
OF
MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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FRACTURES OF THE NECK OF THE FEMUR.

FRACTURES of the neck of the femur have long constituted a serious problem, not only as regards prognosis for restoration of function but for life as well. This fracture, most commonly occurring in the aged has been for many an old individual the unpleasant incident which ushered in a train of factors to terminate life. Long periods of immobilization of the fracture site prove in instances more dangerous than the fracture itself, so that frequently the fracture has been ignored in the hope that death from pneumonia, exhaustion, or decubitus ulcers with associated infection might be prevented.

The following quotation from Smith[44a] in 1854 illustrates the lugubrious viewpoint of his time, a viewpoint which has not been changed universally in our own time:

"Our prognosis in cases of fracture of the neck of the femur must always be unfavorable; in many instances the injury soon proves fatal, and in all the functions of the limb are forever impaired; no matter whether the fracture has taken place within or external to the capsule, whether it has united by ligament or bone, shortening of the limb and lameness are the inevitable results. In forming our prognosis, we must take into account principally the age of the patient, and the situation and nature of the fracture. The results of my own experience would lead me to say, that the form of fracture which is most rapidly and most frequently fatal, is the extracapsular fracture, when it is accompanied by a comminuted fracture with displacement of the trochanters;

but as regards the functions and utility of the limb during the remainder of the patient's life, the intracapsular fracture is the more serious accident, for, independent of the difference which exists between these two varieties of the fracture, as regards the possibility of osseous union, there is likewise a remarkable difference with respect to the ultimate shortening of the limb; for in the extracapsular fracture the amount of shortening which took place when the injury occurred seldom subsequently undergoes any very material increase, but when the fracture is seated within the capsule, absorption of the neck of the bone slowly but steadily proceeds, and an amount of shortening of the limb is thus ultimately produced, equal to, or, in many cases, even greater than the entire length of the neck of the femur.

"In fatal cases death may be owing to a variety of causes: sometimes the patient dies in a few days from the effects of the shock upon a system already enfeebled by age; very frequently bronchitis sets in, and terminates fatally before ten days have elapsed; in other cases the accident is followed by a severe irritative fever, the tongue becomes furred, the bowels constipated, the pulse quick and feeble, and the patient restless and thirsty; he is unable to sleep, and complains much of the pain about the joint; the tongue soon becomes more loaded, the countenance dejected, and expressive of distress and anxiety; the patient begins to talk incoherently, and raves at night, then the pulse fails, the tongue becomes dry and brown, sordes collect about the lips and teeth, the anxiety of countenance and restlessness increase, the bronchial tubes become filled with mucus, a tendency to stupor, or coma, manifests itself, and then death terminates the scene. This form of fever is especially apt to be induced when the injured limb is kept firmly secured in splints and bandages, and maintained in a state of forcible extension."

Likewise Malgaine[33] (1859) expresses the viewpoint of the day with regard to fracture of the neck of the femur:

"The prognosis is always grave; with very rare exceptions, a patient with intra-capsular fracture will be maimed for life, and sometimes even lose the use of the limb entirely. There is besides at the outset a still greater danger to be warded off. . . . The ancient school, still represented by Boyer, held that the want of union in these fractures depended solely on want of contact and of sufficient apparatus; whence they attached great importance to reduction, and contrived a variety of plans for making permanent extension.

"Another school, with Sir Astley Cooper at the head, regarding consolidation as impossible in the immense majority of cases, abandoned all attempts at reduction and all forms of apparatus. 'I should,' says Sir Astley, 'if I sustained this accident in my own person, direct that a pillow should be placed under the limb throughout its length, that another should be rolled up under the knee, and that the limb should be thus extended for ten days or a fortnight, until the inflammation and pain had subsided. I should then daily rise and sit in a high chair, in order to prevent a degree of flexion which would be painful; and walking with crutches, bear gently on the foot at first; then gradually more and more, until the ligament became thickened, and the muscles increased in their power. A high-heeled shoe should be next employed, by which the halt would be much diminished.'"

It might be argued that this is an ancient view of the prognosis and treatment of fractures of the neck of the femur. Several authors in the twentieth century have indicated the futility of treatment of this fracture, not only by intimation but by direct statement. In present day texts the note of futility is to be found. Homans[18] indicates that it is frequently necessary to disregard the fracture and to look after saving the life of the patient. Stimson[48] states that in old people "an ideal anatomic restoration of form is impossible and the surgeon must be content to get union with a shortened neck and probably with changes in the angle which it makes with a shaft." Babcock[2] states that in the aged, death occurs in 17% from intercurrent affections, and bony or firm fibrous union is rather unusual. Ashhurst[1] is hardly more optimistic when he states that 1 out of 5 die in the first year after the injury and in those who recover, a useful limb results in about 7% of cases; nearly all of these have a limp and slight eversion.

Fortunately, the outlook exemplified by the quotation from Sir Astley Cooper is not borne out by the best available statistics of the past 15 years. The work of Royal Whitman[53] brought new hope to the problem, when he showed that it was possible to obtain and maintain reduction of the fragments in intracapsular fractures of the femur. Presented in 1897, Whitman's method of treating fractures of the neck of the femur has been utilized with varying degrees of success. One great deterrent to treatment has been the influence of Sir Astley Cooper[9] who felt that bony union could not take place in fractures of the neck of the femur.

Smith[44b] has written: "In the third volume of Guy's Hospital reports (New Series), there is a paper by Mr. Bransby Cooper upon the causes of the non-union of these fractures, in which he dwells at some length upon the evil which he supposes would result, if osseous union were to occur: he remarks, 'What would have been the result if such union were admitted? That the provisional callus itself would have filled up the acetabulum, and in every way have so interfered with the structure of the joint as in itself to have proved destructive to the performance of every natural function of the limb. My object has been throughout to maintain, that it is ordained by nature that fracture of the neck of the femur, within the capsular ligament, is not to unite by ossific deposition.'"

Smith, however, felt that this opinion was an error and stated that "whenever reparation by bone occurs in the intracapsular fracture, it is owing to the direct union of the broken surfaces and that the effusion of callus around the fragments is by no means essential to the process."

That bony union can and does occur is not now contested. However, for the likelihood of success of union it is necessary for the fragments to be in apposition. Lack of approximation probably accounts for the large number of cases in which non-union results. Whitman has shown that it is possible to obtain approximation and maintain it by abduction technique. Those who have had best results with the Whitman method have adhered to fundamental principles of fracture care, namely, proper adequate reduction, and immobilization. For proper reduction, a general anesthetic is usually necessary. In an elderly patient this is often feared, but as has been pointed out by many, the dangers from a short general anesthesia should be less than the consequences of dis-

comfort from a poorly reduced fracture. For success with the Whitman method, not only must reduction be obtained, but in order to maintain the reduction it is necessary that the extremity be truly abducted on the pelvis. Tilting of the pelvis may at times simulate true abduction.

Löfberg[30] studied a series of 139 cases of intracapsular fractures over the period 1909 to 1922 who were treated by the abduction method. He did not mention the work of Whitman, but his method was similar in detail to the Whitman technique except for the addition of impaction as suggested by Cotton.[10] The study is presented in great detail so that there is little difficulty tracing the results in individual cases. Of the 139 cases, 83 had satisfactory results in that function was restored. In 61 (almost half of the cases) there was complete restoration with no subjective symptoms. Eight cases died as a result of their injury, a mortality of 5.7%. The results recorded by Löfberg, 67% return of function, while not so good as might be hoped for, is much better than might be expected on account of the age of most of these patients. Other authors[6,16b,40,47] have likewise reported a high incidence of good results by use of the Whitman method, but this degree of success is neither universal nor usual. Henderson,[16a] as a result of experience with cases previously treated by others, concludes that the cause for many poor end results is due to improper diagnosis and treatment.

Non-operative methods for treatment of intracapsular fractures of the hip have in common one principle, reduction of the fracture and fixation in abduction and internal rotation. Whether the fixation is by means of plaster as in the cases treated by Whitman and others[40] or by traction,[5,19,34,38,43] good results depend on the ability to hold the fragments of the fractured neck of the femur in apposition by abduction and internal rotation after adequate reduction.

Difficulties associated with the maintenance of reduction have brought about many attempts at fixing the fragments together by operative means. In 1878, Trendelenburg[13] sutured the ends together with wire. König[26] used and recommended this method but for obvious reasons it is not applicable to elderly individuals, despite König's report of its successful use in a man of 70, since it entails an arthrotomy. Likewise the introduction of pegs, spikes, or screws which require opening of the joint is a formidable procedure. Fixation of the fragments with foreign material driven into the bone without opening the joint has likewise been practised sporadically for many years by many authors[12,28,31,36] and while less formidable a procedure, was fraught with many difficulties.

In the use of nails, bolts or screws driven through the neck of the femur to fix the head, disadvantages were associated chiefly with the large amount of foreign material introduced into the bone. Erosion of metal or bone was not uncommon and inflammatory changes within the bone frequent. These difficulties resulted in a rather widespread objection to the use of any type of "hardware" for the fixation of fractures. In 1931, Smith-Petersen and his associates[45] presented a narrow 3-flanged nail for fixation of fractures of the neck of the femur. The nail was strong, and the flanges prevented rotation of the fragments, while the bulk of the pin was not great. The use of rustless steel in the manufacture of modern pins for fixation of fragments is a decided

advance, since steel of high chromium and nickel content apparently causes less reaction in tissues than other steel and is likewise less affected by the tissue fluids.[15]

Smith-Petersen and his associates opened the joint in order to introduce the pin and to effect approximation of the fragments.

Shortly afterward Sven Johannsen[20] made use of the Smith-Petersen nail for fixation of the fragments without opening the joint. Johannsen introduced a wire through the lateral aspect of the femur into the neck, as a guide for the introduction of the larger nail. The direction and position of the wire was determined by Roentgen ray, as was the length of the nail. This technique greatly simplified the procedure and permitted accurate placing of the nail without the necessity of opening the joint. Johannsen introduced the guide wire through the trochanter and into the head of the femur. A great many variations in technique have been devised. These have consisted chiefly in perfection of control of direction of the pin without the necessity of introduction of the guide wire.

Many authors prefer to insert the Smith-Petersen nail under fluoroscopic or radiographic control, without the use of the guide wire or other gadgets designed for direction of the nail.[27,30,37,54] Others use protractors, templates or guides to direct the nail into position.[4,8,11,22–24,41,51]

Some surgeons use multiple small stainless steel pins similar to Kirschner wires, the wires being inserted parallel to each other[25,42] or at various angles.[7,32,35a,b,49] The wires when anchored one to another tend to prevent retraction.

The question as to the need for impaction after reduction as suggested by Cotton[10] is a controversial one. Most authors do not make a special attempt at impaction, but there are those who feel that this is an important adjunct.

The problem of anesthesia is likewise an important consideration. Inhalation anesthesia or spinal anesthesia is advocated by many, chiefly on the basis of the need for adequate relaxation to allow proper reduction. The time necessary for the actual reduction and pinning of the fragments is usually short enough that anesthetic difficulties are not of great magnitude. Others prefer local anesthesia, morphine and scopolamine, or avertin, on the premise that most of the patients are old and do not stand the anesthetic well. We have found, even in the case of a 99-year-old patient with a fracture of the neck of the femur, 50 mg. of novocaine intraspinally to be the anesthetic of choice and no untoward results were noted.

The problem of additional fixation following the apposition of the fragments by pins is widely discussed. Occasionally, the viewpoint is stressed that the patient should be permitted out of bed immediately and allowed to walk. This seems to be expecting a bit too much, although it is frequently advantageous to allow elderly patients out of bed in a wheel chair. However, even this is not usually essential since the patient, with relief of pain which is usual following fixation of the fragments, may be cared for in bed as well as old patients with any other condition. Following the insertion of the pin there is still the necessity for reparative processes before the neck of the femur is strong enough for full weight bearing. Frequently it is advisable, in addition to internal

fixation, to add some form of external fixation. We feel that where this seems advisable, temporary traction has one advantage in that it permits more freedom of motion on the part of the patient.

Difficulties which may arise following the insertion of a pin in the neck of the femur have been noted. Infection due to the pin retracting through the skin has been reported by Rowlette *et al.*[42] and the pin has been found to have migrated into the bladder by Van Ravenswaay[39] and into the pelvis by Backer-Gröndahl[3] and Telson and Ransohoff.[49] However, these accidents are rare. More frequently, the pin tends to loosen and withdraw from the proximal fragment. To overcome this White[52] devised a pin to hold the nail firmly in place and prevent retraction.

The use of various types of screws instead of pins has been revived chiefly on the basis that retraction is prevented. In addition, there are those who hold that the screw has an advantage over the nail because it is possible to draw the proximal fragment more firmly into approximation with the distal fragment.[17,21,29]

During the past 7 years what has been incorrectly termed "blind nailing" has been accepted with enthusiasm. A rather voluminous literature is available. The enthusiasm for this lies in that the procedure is simple enough to permit its use in old debilitated individuals, fixation is assured, active and passive motion is possible, confinement to bed is lessened and due to the necessity for satisfactory reduction before fixation, pain is decreased. These factors have long been recognized as fundamentals in the treatment of fractures and especially in fractures of the neck of the femur.

The method has been widely accepted and many case reports are available. The results appear to be generally better than those obtained with other methods. This may be more apparent than real and one must wait until sufficient general experience has been gained and until adequately and carefully collected statistics are available. In general the outlook is good, since reduction must be obtained if the pin is to be introduced properly. In cases of treatment by fixation in abduction the emphasis all too frequently was placed upon applying the plaster with little regard for adequate reduction. For any method of treatment of fractures of the neck of the femur, fundamental principles demand reduction and fixation. Since adequate reduction is necessary for treatment by pinning or nailing the fragments together, it is quite likely that this most important deficiency, emphasized by Henderson,[16a] with regard to treatment of fractures of the neck of the femur may be overcome.

It is much too early to attempt any evaluation of the end results of modern methods of internal fixation of intracapsular fractures as generally practised. That there will be not only a decreased mortality rate, but a higher incidence of bony union is suggested by the numerous enthusiastic reports now in the literature. However, it is not as yet apparent whether internal fixation will supply the solution to what Speed[46] has so aptly termed the "unsolved fracture." The optimism engendered by glowing reports may cause us to forget that we have long accepted as fact that the nutrition to the neck of the femur was poor

and healing difficult. The introduction of foreign material can only provide immobility of the fragments to permit repair to take place. It is quite possible that by the method of internal fixation with pins or nails the average surgeon may be able to approximate the results obtained by other methods in the best hands and that those more expert will improve their results.

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OPHTHALMOLOGY.

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INTRACRANIAL ANEURYSMS OF THE INTERNAL CAROTID AND OF THE CIRCLE OF WILLIS.

In recent years, the study of aneurysms of the intracranial portion of the internal carotid and of the circle of Willis has assumed gradually increasing importance. Prior to 15 years ago, when Symonds'[9] paper on the subject appeared, the diagnosis of intracranial aneurysm was rarely thought of during the life of the patient. As recently as 1934, Garvey[1] reviewed the clinical symptoms, etiology, and pathologic findings in aneurysms of the circle of Willis and stated that, "the diagnosis of intracranial aneurysm cannot be made with any degree of certainty until rupture occurs." He considered, however, that the clinical syndrome produced by rupture of such an aneurysm was sufficiently characteristic to make diagnosis fairly certain. The use of arteriography offers an opportunity to confirm the diagnosis of an unruptured intracranial aneurysm during the life of the patient, and ligation of the internal carotid offers a possible means of preventing fatal rupture, if the diagnosis can be established. Involvement of vision, of visual fields, and of ocular muscles constitute the presenting symptoms in many of these cases. It is of interest, therefore, to review the ocular changes which suggest at least the possible presence of an intracranial aneurysm and to consider briefly the other diagnostic features which aid in confirming the diagnosis.

The characteristic syndrome of rupture of an intracranial aneurysm is apparently that of a sudden apoplectic seizure with loss of consciousness, vomiting, at times convulsions, followed by severe headache, photophobia, stiffness of the neck, and other signs of meningeal irritation. Examination of the spinal fluid reveals a uniformly bloody fluid under increased pressure. Complete paralysis of the oculomotor nerve with ptosis and iridoplegia is of frequent occurrence and is apparently indicative always of the side of the lesion. Frequently, large hemorrhages are found in the retina, especially around the optic disks. The hemorrhages may be of subhyaloid type and may be seen at times to break through into the vitreous. A mild edema of the optic disks may be present early and may increase in amount if the patient survives the attack. It is not clear why the characteristic hemorrhages in the retina are absent in some cases. But when they are present in

a patient who has had a sudden onset of coma followed by severe headache, the suspicion of hemorrhage into the subarachnoid space should always be aroused. The mechanism of these hemorrhages into the retina is not definitely known. Originally they were thought to be due to the extravasation of blood along the sheath of the optic nerve through the lamina cribrosa into the retina. However, Riddoch and Goulden[7] have shown that the hemorrhages in the retina are due to obstruction of the central vein of the retina in the optic sheath with venous stasis in the retina and, at times, actual rupture of the walls of the retinal veins.

With the rather definite establishment of this syndrome of the ruptured aneurysm, more interest has centered recently on the possibility of diagnosis of the unruptured aneurysm. In 1925, Foster Moore[8] reported what he believed to be the first case of unruptured intracranial aneurysm diagnosed during the life of the patient. This was a mycotic aneurysm which occurred during the course of a malignant endocarditis and which was found to involve the end of the right internal carotid artery and the beginnings of the anterior cerebral, posterior communicating, and ophthalmic arteries. The aneurysm had caused sudden, complete blindness in the right eye through rupture of the right optic nerve. Twelve days later there was an additional defect in the upper temporal field of the left eye.

A number of individual case reports have appeared in the literature from time to time, all of which are summarized in Jefferson's paper published in 1937. Most of these cases were diagnosed at operation or autopsy. As representative of various types of vision and field changes which may be encountered, the cases of Foster Kennedy,[3] of Wetzel,[10] and of McKendree and Doshay[4] may be cited here. Kennedy reported a case simulating bilateral retrobulbar neuritis in which the loss of vision in the right eye preceded by 6 months that in the left eye. At exploration, the mass found was thought to be a glioma. Death occurred, however, following a rupture of the aneurysm which was found at necropsy in the right internal carotid artery. In Wetzel's case, there was secondary optic atrophy in the left eye with vision reduced to 6/60 and with progressive concentric contraction of the visual field. At necropsy, which in this case also followed rupture of the aneurysm, the left optic nerve was found markedly stretched and flattened over the surface of a large aneurysm of the left internal carotid artery.

In the 3 cases reported by McKendree and Doshay, the ocular findings were those of progressive chiasmal lesions with bitemporal hemianopic field defects. All of these cases were discovered at operation following the diagnosis of chiasmal lesions of indeterminate type. In 1 of the cases, the presence of the aneurysm was confirmed at necropsy following rupture. In another case, exploratory craniotomy revealed an aneurysm of the left internal carotid artery. Following a period of digital compression, the left common and internal carotid arteries were ligated. The left eye had been blind before the operation and remained so, but the temporal field of the right eye had widened out considerably 3 months after the ligation. In 1 of the cases, Roentgenograms of the

skull were negative; in 1, erosion of the sella and clinoid processes was present; in the third, there was decalcification of the dorsum sellæ. In all of the cases, encephalographic studies demonstrated the site of the lesion but not its nature.

With the aid to diagnosis furnished by careful and expert roentgenographic studies, encephalographic studies, and arteriograms, it is becoming possible to diagnose at least a certain percentage of cases of unruptured intracranial aneurysm during life. In 1926, Sosman and Vogt[8] called attention to the roentgenographic diagnosis of aneurysms of the internal carotid artery and the circle of Willis. They said, "The recognition of these aneurysms on Roentgen examination is by means of (1) calcification in the wall of the aneurysm, or (2) erosion of the bone adjacent to the aneurysmal sac. In the first, one can see thin plaques of calcium, usually semilunar in shape, with their convexity upward, lying beside the sella, or should the aneurysm be large, rising above the level of the sella, but just to one side of it. These are fine curvilinear shadows, sharply outlined, occasionally segmented, and easily recognizable as being in the wall of a cystic or rounded structure. . . . . The erosion due to these pulsating sacs . . . . involves or may involve one anterior clinoid, the lateral half of the body of the sphenoid on the same side, and a similar portion of the posterior clinoid. . . . . There is no expansion of the pituitary fossa . . . . and no apparent depression of the floor of the fossa. The opposite anterior clinoid is not involved . . . . and there is no pressure atrophy or forward bending of the posterior clinoid."

Sosman and Vogt admitted that roentgenographic diagnosis was not uniformly successful in the cases they reported. They estimated that in 25% of the cases, diagnosis was possible from the roentgenographic findings and that, in an additional 25%, the roentgenographic findings would support the clinical impression. They expressed the belief that with improvement of technique, roentgenographic diagnosis would be possible in a higher percentage of cases. This belief would seem to be supported by the results in a more recent series of cases, that of McKinney, Acree and Soltz.[5]

In 1936, McKinney, Acree and Soltz reported 8 cases of unruptured aneurysm of the intracranial portion of the internal carotid artery proximal to the point where it leaves the roof of the cavernous sinus. All of them had paralysis of the third and fourth nerves, 6 had paralysis of the sixth nerve, 5 had exophthalmos on the side of the lesion, 4 had pallor of the disk, 2 had low-grade papilledema, 1 was blind, and 5 had contracted fields on the side of the lesion. All had corneal anesthesia and pain and paresthesias over the eye. They consider that the clinical syndrome of an unruptured aneurysm of the intracranial portion of the internal carotid artery consists of exophthalmos and a partial or complete involvement of the second, third, fifth and sixth nerves on the side of the aneurysm. The third and fifth nerves are involved, always, the others usually. Since the internal carotid artery gives off branches in the cavernous sinus to the third, fourth, sixth and first divisions of the fifth nerve, the paralysis may be on a vascular as well as a pressure basis. Aneurysms in this location may extend into the

ophthalmic artery but such extension is not necessary to produce the syndrome described. All of their cases had confirmatory roentgenographic findings. In addition to the curvilinear plaques of calcification and the unilateral erosion of the sella described by Sosman and Vogt, they called attention to the presence of enlargement of the sella, unilateral enlargement of the optic foramen and of the superior orbital fissure, erosion of the margins of the carotid canal, and displacement of the pineal.

Jefferson[2] agrees substantially with McKinney, Acree and Soltz on the roentgenographic diagnostic signs of intracranial carotid aneurysms. He calls attention also to the value of angiography in definitely localizing the aneurysm. He has divided his 53 intracranial aneurysms into four groups: (1) Pure subarachnoid hemorrhage with nothing to indicate the precise site of the aneurysm, 16 cases; (2) aneurysms with paralysis of cranial nerves, usually the third, 9 cases; (3) sacular (nonfistulous) aneurysms of the internal carotid in the cavernous sinus, 16 cases; and (4) basal aneurysms with affection of the visual pathways, 12 cases. His paper is devoted essentially to the detailed consideration of the 12 cases in the last group, in which, as in the third group, the symptoms of the aneurysm are essentially those of a tumor.

Jefferson thinks that the most important division of carotid aneurysms is into supraclinoid and infraclinoid. The infraclinoid aneurysms arise in the cavernous sinus and give rise to ophthalmoplegia and disturbances of the trigeminal nerve. Visual difficulty is caused essentially by paralysis of accommodation or by diplopia. Supraclinoid aneurysms spring from the carotid at the origin of the ophthalmic or posterior communicating arteries or at the final bifurcation of the main trunk. These are the aneurysms which interfere primarily with vision. Jefferson further subdivides them into four groups: (1) Those interfering with the optic radiation and striate cortex, 3 cases; (2) those compressing the optic tract, 1 case; (3) those affecting the optic nerves, 2 cases; and (4) those involving the chiasma, 6 cases.

In the first group, Jefferson includes cases of homonymous hemianopsia following subarachnoid hemorrhage. He believes that the hemianopsia is the result of thrombosis of the posterior or middle cerebral artery following the rupture of an aneurysm. Jefferson considers as indicative of pressure on the optic tract a left homonymous hemianopsia which was found in association with a right third nerve paralysis and a left hemiparesis in an aneurysm of the right posterior cerebral artery immediately outside the third nerve confirmed at necropsy following death from rupture of the aneurysm. Of the 2 cases with unilateral loss of vision, the onset was gradual in 1 and sudden in the other. The case with gradual loss of vision was proved at necropsy to be due to a large aneurysm of the internal carotid artery in the anterior end of the cavernous sinus. Both these cases also had paralysis of the third nerve on the side of the lesion. Wetzel calls attention to the fact that this unilateral loss of vision is due to the fact that the optic nerve rests inferiorly on the internal carotid artery at the point at which the latter forms an arch with the convexity upward and gives origin to the ophthalmic artery.

Of Jefferson's 6 cases with signs of compression of the chiasm, 3 showed bitemporal hemianopsia, 1 was blind in one eye with temporal hemianopsia in the other eye, 1 had bilateral inferior altitudinal anopsia with relative bitemporal hemianopsia, and 1 had unilateral central scotoma with relative bitemporal hemianopsia. Four of these cases were confirmed by operation and 2 by angiograms with thorotrast. It is of interest that in 2 of these cases the eye on the side opposite to the aneurysm showed the earliest and greatest loss of vision.

Jefferson thinks that pain and headache are more frequent and symptoms severe in patients with aneurysms than in those with pituitary tumors. The characteristic anesthesia of the ophthalmic division of the fifth nerve which is so frequent in subclinoid aneurysms does not occur in supraclinoid aneurysms. Hemiparesis is rare. Mental changes are frequent. Paralyses of the ocular muscles occur in supraclinoid aneurysms but are not as frequent as in the subclinoid type. Anosmia is very infrequent. Hypothalamic signs and evidences of dyspituitarism are rather rare.

Ligation of the carotid is gradually being recognized as the only valuable method of treatment for cases of intracranial carotid aneurysms. Jefferson believes that this is true in spite of the fact that he ligated only 1 of the cases in the present series (with definite improvement in vision). Because of the risks involved in ligation of the carotid, he thinks that only those cases should be ligated in which there is progressive failure of vision or persistent pain. Before ligation, it should be demonstrated that digital compression for 30 minutes is tolerated without ill-effect. It is well, Jefferson thinks, to do the ligation under local anesthesia so that the effects of a temporary ligature can be observed for a full hour before the final ligature is applied. It should be remembered, however, that even this procedure does not always prevent the development of a hemiplegia or aphasia 36 to 48 hours after the ligation.

Summary. It seems rather obvious that there are two relatively distinct locations of intracranial aneurysms in which the types of ocular involvement are at least relatively if not entirely distinct. Saccular aneurysms of the internal carotid in the cavernous sinus or just at the point of exit produce essentially oculomotor paralyses. Aneurysms of the internal carotid at the point of origin of the various branches of the circle of Willis or of the ophthalmic artery produce ocular syndromes of chiasmal or prechiasmal type with characteristic field defects. Aneurysms which cause primarily oculomotor rather than visual field defects seem to be the ones most frequently associated with recurrent hemorrhages into the subarachnoid space and retina. Aneurysms in this location probably respond more favorably in the main to ligation of the carotid than do aneurysms located higher in the circle of Willis. Paralysis of the third nerve is a more reliable localizing sign of the side of the aneurysm than is the character of the defects in the visual fields, unless the loss of vision is entirely unilateral.

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